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FINAL PILOT REPORT

Study Title

ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

Data Requirement

U.S. Environmental Protection Agency
Pesticide Assessment Guidelines
Subdivision F, 83-3

U.S. Environmental Protection Agency
Toxic Substances Control Act Test Guidelines -
Health Effects Testing Guidelines - 798.4900

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Performing Laboratory

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Laboratory Project ID

Argus Research Laboratories, Inc., Protocol Number: 1416-002P

GOOD LABORATORY PRACTICE STATEMENT

This study was conducted according to U.S. Environmental Protection Agency (EPA FIFRA/TSCA) *Good Laboratory Practice Standards; Final Rule* (40 CFR Part 160/792), the Japanese Ministry of Agriculture, Forestry and Fisheries (MAFF) *Good Laboratory Practice Standards* (59 NohSan No. 3850), and the Organization for Economic Cooperation and Development (1992), *The OECD Principles of Good Laboratory Practice*, Environment Monograph No. 45. Any areas of noncompliance are documented in the study record. No deviations existed that significantly affected the validity of the study.

Raymond G. York, Ph.D., DABT — Date
Associate Director of Research and
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Argus Research Laboratories, Inc.

PROTOCOL 1416-002P: ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

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TITLE: ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

ARGUS RESEARCH LABORATORIES, INC.
PROTOCOL NUMBER: 1416-002P

ABSTRACT

Twenty-five pregnant New Zealand White [Hra:(NZW)SPF] rabbits were randomly assigned to five exposure groups, five rabbits per group. The test substance, ammonium perchlorate, was administered orally via the drinking water daily *ad libitum* to these naturally bred female rabbits on days 6 through 28 of presumed gestation (DGs 6 to 28) at target dosages of 0 (Carrier), 0.1/50, 1.0/100, 10.0 and 20.0 mg/kg/day (Groups 1, 2, 3, 4 and 5, respectively). The carrier was reverse osmosis membrane processed deionized water (R.O. deionized water). The drinking water concentrations of the ammonium perchlorate were initially 0, 0.96, 9.75, 95.75 and 191 µg/mL, based on body weights recorded on DG 5 and an estimated water consumption value of 100 mL/kg/day, and were adjusted subsequently on the basis of the actual body weight and water consumption values. On DG 13, the target dosages for Groups 2 and 3 were increased to 50 and 100 mg/kg/day, respectively, in order to establish evidence of maternal toxicity.

Checks for viability were made at least twice daily during the study. Clinical observations were recorded daily during dosage period and on the day of sacrifice. Body weights and feed and water consumption values were recorded daily during the study. The rabbits were anesthetized on DG 29, followed by blood collection and exsanguination. Approximately 3 mL of blood was collected and shipped for analysis of TSH, T_3 and T_4 levels. The rabbits were examined for number and distribution of corpora lutea, implantation sites and uterine contents. A gross necropsy of the thoracic, abdominal and pelvic viscera was performed, and the gravid uterine weight was recorded. Fetuses were weighed, examined for gross external alterations, and examined internally to determine

sex. The thyroid gland with the parathyroid gland was trimmed and weighed after fixation and these tissues were examined histologically.

No deaths, abortions or premature deliveries occurred during this study. All clinical observations were considered unrelated to the test article. There were no gross necropsy observations for rabbits at Caesarean-sectioning. Absolute and relative thyroid/parathyroid weights were reduced in Group 5 and increased in Group 4, as compared to the control value. There were no biologically important differences in average maternal body weights, body weight gains, gravid uterine weights, corrected maternal body weights (DG 29 body weight minus the gravid uterine weight), or corrected maternal body weight changes between the treated groups and the control group prior to increasing the target dosage for Groups 2 and 3 (DGs 6 to 13), after increasing the target dosage for Groups 2 and 3 (DGs 13 to 29) or over the entire exposure period (DGs 6 to 29). There were also no biologically important differences in average maternal absolute and relative water or feed consumption between the treated groups and the control group over the same study intervals. The control group had the lowest average terminal body weights, absolute water consumption and absolute and relative feed consumption values of the five exposure groups.

Exposure to ammonium perchlorate at target dosages as high as 100 mg/kg/day on DGs 13 to 29 or as high as 20.0 mg/kg/day on DGs 6 to 29 did not affect DG 29 Caesarean-sectioning parameters. Three fetuses in the 20.0 mg/kg/day exposure group had external alterations at gross examination. Two fetuses were malformed with meningocele, umbilical hernia and absent tail, or cleft palate, whole body edema, head disconnected from spinal column, absent forelimbs, spleen, right ovary and ventral thoracic wall, liver adhesions and all thoracic and abdominal viscera external to body cavity. The third fetus had ascites.

The 100 mg/kg/day target dosage group had reduced average serum T_3 and T_4 levels, relative to the control group. Average serum levels of TSH were also reduced in the 100 mg/kg/day target dosage group, however, the level of TSH in the 10.0 mg/kg/day target dosage group was most reduced of all the treated groups. Treatment-related microscopic changes were observed in the thyroid gland of rabbits in the 20.0, 50 and 100 mg/kg/day dosage groups. The treatment-related effects consisted primarily of hypertrophy of the follicular epithelial cells. These follicles with the enlarged cells were decreased in size and contained a decreased amount of pale, vacuolated colloid. Another finding seen only in the 50 mg/kg/day dosage group was enlarged, cystic and irregularly shaped follicles in two of the five rabbits.

I. Purpose:

The purpose of this study was to provide information for the selection of dosages to be used in the developmental toxicity (embryo-fetal toxicity and teratogenic potential) study of ammonium perchlorate administered orally via drinking water to New Zealand White [Hra:(NZW)SPF] presumed pregnant female rabbits.

II. Methods[a]:

Twenty-five timed pregnant New Zealand White [Hra:(NZW)SPF] rabbits were randomly assigned to five exposure groups, five rabbits per group. The test substance, ammonium perchlorate (lot 03907LF), was received on August 28, 1997 and December 29, 1997, from Aldrich Chemical Company (Milwaukee, Wisconsin) and stored at room temperature. The test substance was administered orally via the drinking water daily *ad libitum* to these naturally bred female rabbits on days 6 through 28 of presumed gestation (DGs 6 to 28) at target dosages of 0 (Carrier), 0.1/50, 1.0/100, 10.0 and 20.0 mg/kg/day (Groups 1, 2, 3, 4 and 5, respectively). The carrier was reverse osmosis membrane processed deionized water (R.O. deionized water). The drinking water concentrations of the ammonium perchlorate were initially 0, 0.96, 9.75, 95.75 and 191 µg/mL, based on body weights recorded on DG 5 and an estimated water consumption value of 100 mL/kg/day, and were adjusted subsequently on the basis of actual body weight and water consumption values. On DG 13, the target dosages for Groups 2 and 3 were increased to 50 and 100 mg/kg/day, respectively, in order to establish evidence of maternal toxicity.

Checks for viability were made at least twice daily during the study. Clinical observations were recorded daily during the dosage period and on the day of sacrifice. Body weights and feed and water consumption values were recorded on daily during the study.

The rabbits were anesthetized on DG 29, followed by blood collection and exsanguination. Approximately 3 mL of blood was collected from the vena cava of each doe. The serum was aliquoted into three vials for analyses of TSH, T_3

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a. Detailed descriptions of all procedures used in the conduct of this study are provided in the appropriate sections of this report and in the attached protocol and amendments. Deviations from the protocol are available in the raw data.

and T_4 levels by Ani Lytics, Inc., Gaithersburg, Maryland. The rabbits were examined for number and distribution of corpora lutea, implantation sites, live and dead fetuses and early and late resorptions. A gross necropsy of the thoracic, abdominal and pelvic viscera was performed, and the gravid uterine weight was recorded. Fetuses were weighed, examined for gross external alterations, and examined internally to determine sex. Fetuses with gross alterations were retained.

The thyroid gland with the parathyroid gland and a section of the trachea were excised and immersed in fixative. After at least 48 hours fixation, the thyroid with the parathyroid samples were trimmed and weighed. Tissue samples were shipped to Research Pathology Services, Inc., New Britain, Pennsylvania, for histopathological evaluation.

III. Results:

A. Consumed Dosages (Summary - Table 1)

The concentration of ammonium perchlorate in the drinking water was changed twice during the study conduct; once on DG 13 when the target dosages of Groups 2 and 3 were increased and the concentrations for Groups 1, 4 and 5 were adjusted to reflect the body weights and drinking patterns of the does, and again on DG 20 when the concentrations for Groups 1 through 5 were adjusted for body weight and water consumption values. Actual consumed dosages on DGs 6 to 13 were 0, 0.1, 0.9, 7.5 and 18.2 mg/kg/day for the 0 (Carrier), 0.1, 1.0, 10.0 and 20.0 mg/kg/day target dosage groups, respectively. Actual consumed dosages on DGs 13 to 20 were 0, 10.4, 20.1, 66.8 and 106.8 mg/kg/day for the 0 (Carrier), 10.0, 20.0, 50 and 100 mg/kg/day target dosage groups, respectively. Actual consumed dosages on DGs 20 to 29 were 0, 9.4, 15.6, 46.6 and 68.2 mg/kg/day for the 0 (Carrier), 10.0, 20.0, 50 and 100 mg/kg/day target dosage groups, respectively.

B. Mortality, Clinical and Necropsy Observations (Summary - Table 2; Individual Data - Tables 13 and 14)

No deaths, abortions or premature deliveries occurred during this study.

All clinical observations were considered unrelated to the test article because: 1) the incidences were not dosage-dependent; and 2) they are commonly seen in rabbits in the laboratory environment. These observations included localized

alopecia of the underside and abnormal stool (soft or liquid feces and scant feces in cage pan).

There were no gross necropsy observations for rabbits at Caesarean-sectioning.

C. Terminal Body Weights and Thyroid/Parathyroid Weights and Ratios (%) Of Thyroid/Parathyroid To Terminal Body Weight (Summary - Table 3; Individual Data - Table 15)

The control group had the lowest average terminal body weights of the five exposure groups. Absolute and relative thyroid/parathyroid weights were reduced in Group 5 and increased in Group 4, as compared to the control value.

D. Maternal Body Weights, Gravid Uterine Weight and Body Weight Changes (Figure 1; Summaries - Tables 4 and 5; Individual Data - Table 16)

There were no biologically important differences in average maternal body weights, body weight gains, gravid uterine weights, corrected maternal body weights (DG 29 body weight minus the gravid uterine weight) or corrected maternal body weight changes between the treated groups and the control group prior to increasing the target dosage for Groups 2 and 3 (DGs 6 to 13), after increasing the target dosage for Groups 2 and 3 (DGs 13 to 29) or over the entire exposure period (DGs 6 to 29). The control group had the lowest average body weights and gravid uterine weights of the five exposure groups on DG 29.

E. Maternal Absolute (g/day) and Relative (g/kg/day) Water Consumption Values (Figure 2; Summaries - Tables 6 and 7; Individual Data - Table 17)

There were no biologically important differences in average maternal absolute or relative water consumption between the treated groups and the control group prior to increasing the target dosage for Groups 2 and 3 (DGs 6 to 13), after increasing the target dosage for Groups 2 and 3 (DGs 13 to 29) or over the entire exposure period (DGs 6 to 29). The control group had the lowest absolute water consumption of the five exposure groups over DGs 2 to 29.

F. Maternal Absolute (g/day) and Relative (g/kg/day) Feed Consumption Values (Summaries - Tables 8 and 9; Individual Data - Table 18)

There were no biologically important differences in average maternal absolute or relative feed consumption between the treated groups and the control group

prior to increasing the target dosage for Groups 2 and 3 (DGs 6 to 13), after increasing the target dosage for Groups 2 and 3 (DGs 13 to 29) or over the entire exposure period (DGs 6 to 29). The lowest absolute and relative feed consumption values occurred in the control and 10.0 mg/kg/day target dosage groups for the entire exposure period (DGs 6 to 29).

G. Caesarean-Sectioning and Litter Observations (Summaries - Tables 10 and 11; Individual Data - Tables 19 through 21)

All does were pregnant. Caesarean-sectioning observations were based on four or five pregnant does in each of Groups 1 through 5. One doe in the control dosage group had a unilateral pregnancy resulting in three live fetuses. Because such occurrences can skew the distribution of the data, Caesarean-sectioning and litter observations data were summarized excluding the values for this doe and litter.

Exposure to ammonium perchlorate at target dosages as high as 100 mg/kg/day on DGs 13 to 29 or as high as 20.0 mg/kg/day on DGs 6 to 29 did not affect DG 29 Caesarean-sectioning parameters. The litter averages for corpora lutea, implantations, litter sizes, live fetuses, early and late resorptions, percent does with resorbed conceptuses, percent male fetuses, fetal body weights and the percent resorbed conceptuses, as well as the numbers of does with viable fetuses, were comparable among the five exposure groups. All placentae appeared normal. No doe had a litter consisting of only resorbed conceptuses and there were no dead fetuses.

H. Fetal Alterations (Summary - Table 12; Individual Data - Table 21)

Fetal evaluations were based on 32, 38, 40, 38 and 41 rabbit fetuses from the five dosage groups, respectively. Each of these fetuses was examined for gross external alterations. Three fetuses in the 20.0 mg/kg/day exposure group were observed to have external alterations at gross examination.

Fetus 6747-3 had a meningocele, an umbilical hernia with a portion of the liver and intestines protruding and an absent tail.

Fetus 6748-3 had a cleft palate, whole body edema, head disconnected from spinal column, absent forelimbs, spleen, right ovary and ventral thoracic wall, the liver adhered to the small intestines and thymus, and all thoracic and abdominal viscera external to body cavity.

Fetus 6749-1 had a distended abdomen that proved to be ascites when opened to internally sex the fetus.

The three does in the 20.0 mg/kg/day exposure group that produced litters with malformed fetuses were sired by three different bucks.

I. Thyroid Hormone Levels (ATTACHMENT 2)

The 100 mg/kg/day target dosage group had reduced average serum T_3 and T_4 levels, relative to the control group. Average serum levels of TSH were also reduced in the 100 mg/kg/day target dosage group, however, the level of TSH in the 10.0 mg/kg/day target dosage group was most reduced of all the treated groups. Serum T_3 levels were 141.432, 112.028, 112.888, 127.906 and 83.546 ng/dL, and T_4 levels were 1.842, 0.936, 1.148, 1.004 and 0.828 µg/dL in the 0 (Carrier), 10.0, 20.0, 50 and 100 mg/kg/day target dosage groups. TSH levels were 0.820, 0.384, 0.600, 0.756 and 0.532 ng/mL in these same respective dosage groups.

J. Thyroid Histopathology (ATTACHMENT 3)

Treatment-related microscopic changes were observed in the thyroid gland of rabbits in the 20.0, 50 and 100 mg/kg/day dosage groups. The treatment-related effects consisted primarily of hypertrophy of the follicular epithelial cells. These follicles with the enlarged cells were decreased in size and contained a decreased amount of pale, vacuolated colloid. Another finding seen only in the 50 mg/kg/day dosage group was enlarged, cystic and irregularly shaped follicles in two of the five rabbits.

There were no treatment-related microscopic changes in the thyroid gland of any of the rabbits given 10.0 mg/kg/day of ammonium perchlorate during gestation.

IV. Conclusion:

There is an apparent paradox that the three malformed fetuses were in the 20.0 mg/kg/day exposure (Group 5), whereas higher target dosages of 50 and 100 mg/kg/day (Groups 2 and 3, respectively) produced all externally normal fetuses.

A possible explanation is that ammonium perchlorate caused the malformations early in the gestational period (before DG 13, the day the target dosages for Groups 2 and 3 were increased from 0.1 and 1.0 to 50 and 100 mg/kg/day,

respectively). Does in Groups 2 and 3 were exposed to 0.1 and 1.0 mg/kg/day ammonium perchlorate on DGs 6 to 12 and then to 50 and 100 mg/kg/day on DGs 13 to 29, whereas does in Group 5 were exposed to 20.0 mg/kg/day during the entire dosage period (DGs 6 to 29). The increase in the targeted dosages occurred after a portion of the critical period for organogenesis had occurred.

An alternative explanation is that the malformations were spontaneous and unrelated to the ammonium perchlorate exposure. It is a reasonable possibility that the malformations were spontaneous, given that fetal body weights were not reduced in the 20.0 mg/kg/day target dosage group (a hallmark of a developmental toxicant) and that the types of malformations that occurred were different in each fetus, apparently not caused by the same mechanism of action.

In either case, it is recommended that in the full study the 20.0 mg/kg/day target dosage should be repeated along with two dosages lower than 20.0 mg/kg/day and one higher than 20.0 mg/kg/day using 20 does per group.

Based on the results of this study, target dosages of 0 (Carrier), 0.1, 1.0, 20.0 and 50.0 mg/kg/day of ammonium perchlorate in the drinking water are recommended for the developmental toxicity study in rabbits. The 0.1 mg/kg/day dosage is expected to be a no-observable-adverse-effect-level (NOAEL) for both maternal and embryo-fetal toxicity, and the 50.0 mg/kg/day dosage is expected to produce minimal maternal and developmental toxicity.

10-Dec 98

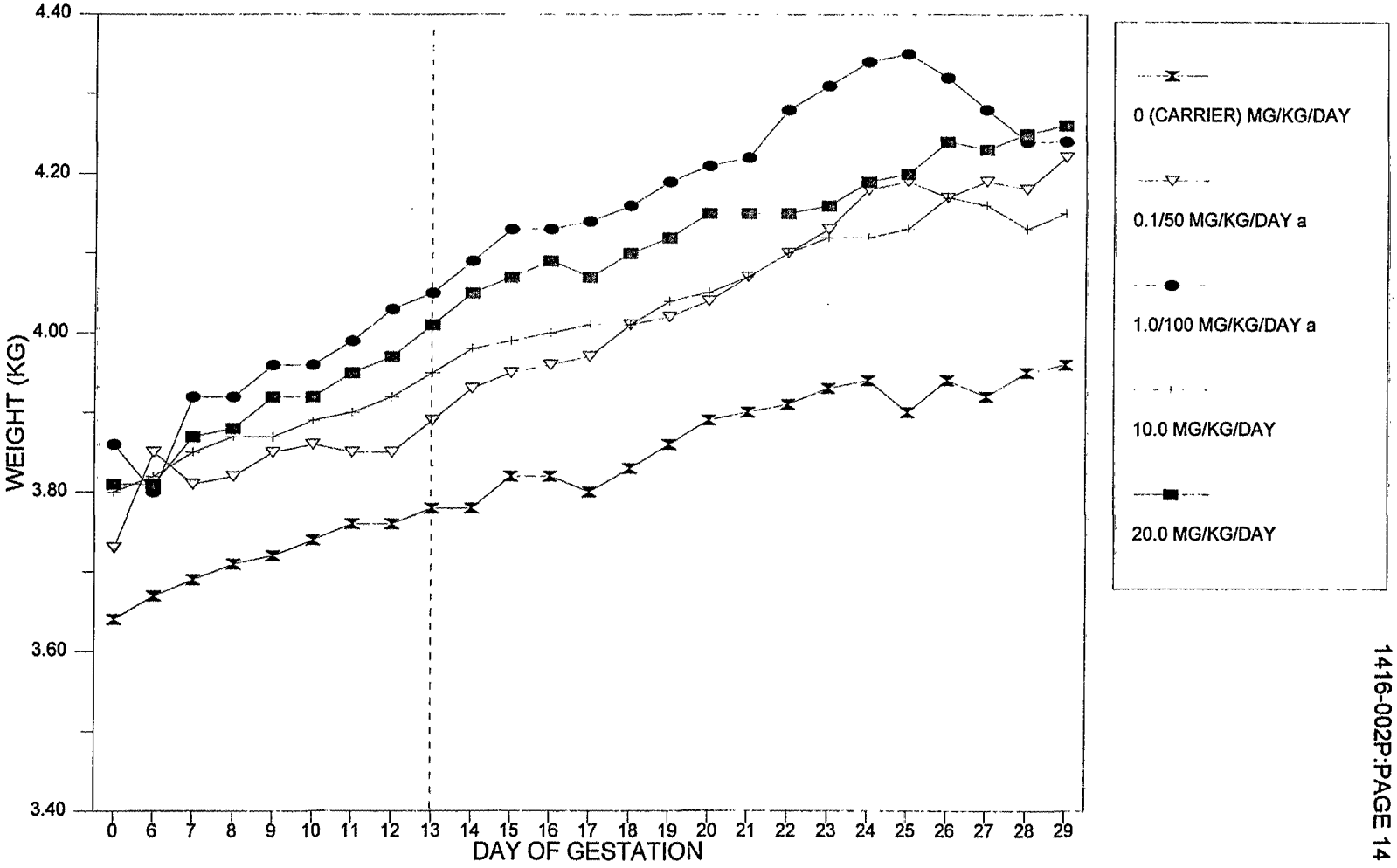
Alan M. Hoberman, Ph.D., DABT Date
Director of Research

10-DEC-98

Raymond G. York, Ph.D., DABT Date
Associate Director of Research
and Study Director

MATERNAL BODY WEIGHTS

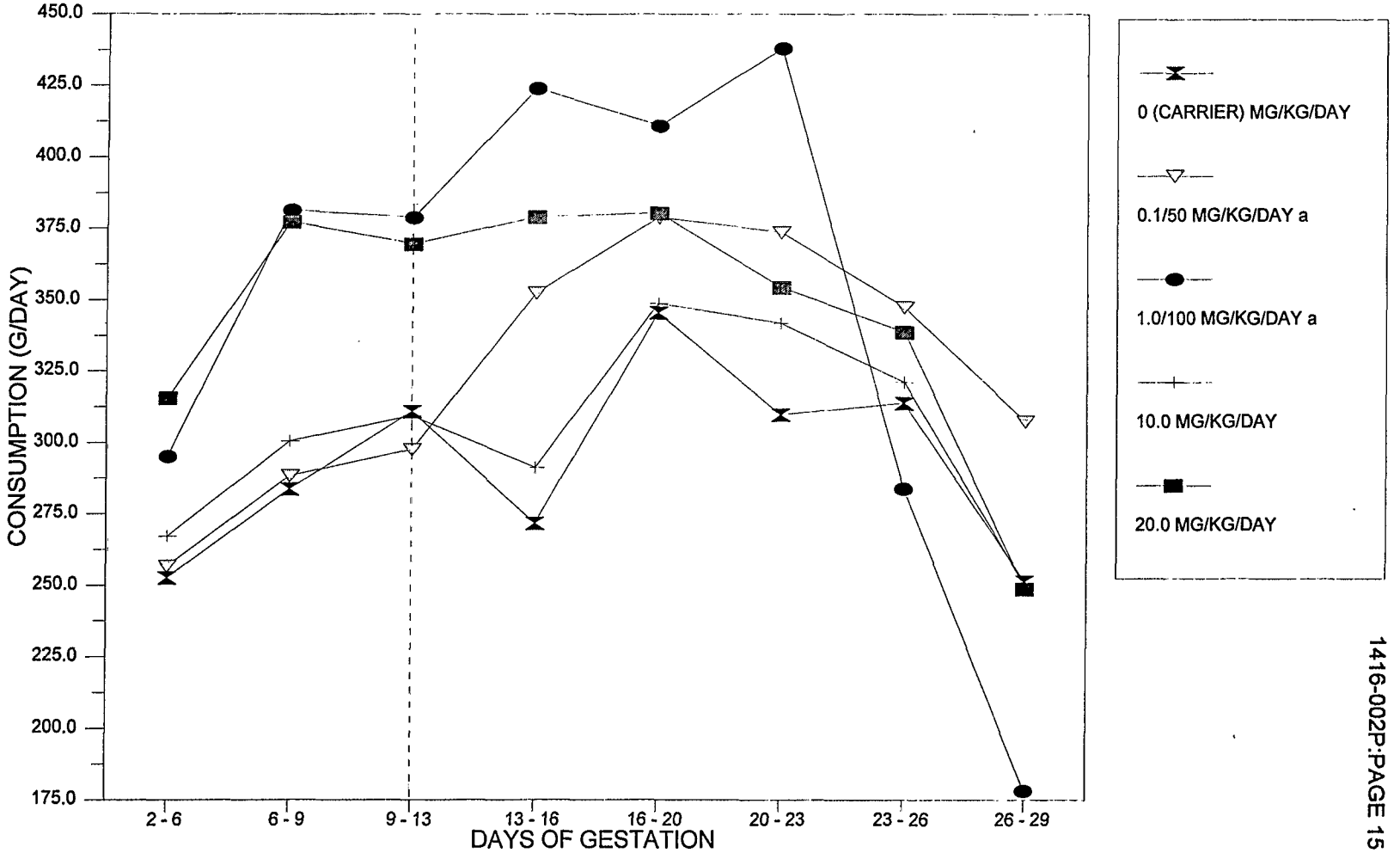
Figure 1



a. The target dosage levels of groups 2 and 3 were increased from 0.1 mg/kg/day and 1.0 mg/kg/day to 50 mg/kg/day and 100 mg/kg/day, respectively on day 13 of gestation.

MATERNAL ABSOLUTE WATER CONSUMPTION

Figure 2



a. The target dosage levels of groups 2 and 3 were increased from 0.1 mg/kg/day and 1.0 mg/kg/day to 50 mg/kg/day and 100 mg/kg/day, respectively on day 13 of gestation.

PROTOCOL 1416-002P: ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

TABLE 1 (PAGE 1): CONSUMED DOSAGES (MG/KG/DAY) - SUMMARY

DOSAGE GROUP TARGET DOSAGE (MG/KG/DAY)a		1 0 (CARRIER)	2 0.1/50b	3 1.0/100b	4 10.0	5 20.0
RABBITS TESTED	N	5	5	5	5	5
PREGNANT	N	5	5	5	5	5
MATERNAL ACTUAL DOSAGE (MG/KG/DAY)						
DAYS 6 - 9	MEAN±S.D.	0.0 ± 0.0	0.1 ± 0.0	1.0 ± 0.1	7.5 ± 0.9	18.6 ± 5.4
DAYS 9 - 13	MEAN±S.D.	0.0 ± 0.0	0.1 ± 0.0	0.9 ± 0.2	7.6 ± 0.7	17.8 ± 3.5
DAYS 6 - 13	MEAN±S.D.	0.0 ± 0.0	0.1 ± 0.0	0.9 ± 0.2	7.5 ± 0.7	18.2 ± 4.3
DAYS 13 - 16	MEAN±S.D.	0.0 ± 0.0	64.4 ± 12.2	109.8 ± 30.8	9.4 ± 1.0	20.2 ± 4.2
DAYS 16 - 20	MEAN±S.D.	0.0 ± 0.0	68.5 ± 17.5	104.6 ± 20.3	11.2 ± 1.2	19.9 ± 4.3
DAYS 13 - 20	MEAN±S.D.	0.0 ± 0.0	66.8 ± 14.5	106.8 ± 23.9	10.4 ± 0.5	20.1 ± 4.2
DAYS 20 - 23	MEAN±S.D.	0.0 ± 0.0	51.8 ± 14.3	100.3 ± 24.6	10.6 ± 1.6	17.9 ± 4.5
DAYS 23 - 26	MEAN±S.D.	0.0 ± 0.0	46.8 ± 8.5	63.9 ± 22.7	9.8 ± 2.0	16.9 ± 5.6
DAYS 26 - 29	MEAN±S.D.	0.0 ± 0.0	41.2 ± 13.6	40.3 ± 23.5	7.7 ± 4.0	12.2 ± 4.8
DAYS 20 - 29	MEAN±S.D.	0.0 ± 0.0	46.6 ± 10.1	68.2 ± 22.0	9.4 ± 2.4	15.6 ± 4.8

DAYS = DAYS OF GESTATION

a. Dosage occurred on days 6 through 28 of gestation.

b. The target dosage levels of Groups 2 and 3 were increased from 0.1 mg/kg/day and 1.0 mg/kg/day to 50 mg/kg/day and 100 mg/kg/day, respectively on day 13 of gestation.

PROTOCOL 1416-002P: ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

TABLE 2 (PAGE 1): CLINICAL AND NECROPSY OBSERVATIONS - SUMMARY

DOSAGE GROUP TARGET DOSAGE (MG/KG/DAY)a	1 0 (CARRIER)	2 0.1/50b	3 1.0/100b	4 10.0	5 20.0
MAXIMUM POSSIBLE INCIDENCE	120/ 5	120/ 5	120/ 5	120/ 5	120/ 5
MORTALITY	0	0	0	0	0
SCANT FECES	0/ 0	0/ 0	4/ 2	1/ 1	0/ 0
SOFT OR LIQUID FECES	0/ 0	1/ 1	2/ 1	0/ 0	0/ 0
LOCALIZED ALOPECIA: UNDERSIDE	0/ 0	3/ 1	0/ 0	0/ 0	0/ 0
WITH THE EXCEPTION OF PERSISTENT ADVERSE CLINICAL OBSERVATIONS, NO ADDITIONAL GROSS LESIONS WERE IDENTIFIED AT NECROPSY					

MAXIMUM POSSIBLE INCIDENCE = (DAYS x RABBITS)/NUMBER OF RABBITS EXAMINED PER GROUP ON DAYS 6 THROUGH 29 OF PRESUMED GESTATION.
N/N = TOTAL NUMBER OF OBSERVATIONS/NUMBER OF RABBITS WITH OBSERVATION.

a. Dosage occurred on days 6 through 28 of gestation.

b. The target dosage levels of Groups 2 and 3 were increased from 0.1 mg/kg/day and 1.0 mg/kg/day to 50 mg/kg/day and 100 mg/kg/day, respectively on day 13 of gestation.

PROTOCOL 1416-002P: ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

TABLE 3 (PAGE 1): TERMINAL BODY WEIGHTS AND THYROID/PARATHYROID WEIGHTS AND RATIOS (%) OF THYROID/PARATHYROID WEIGHT TO TERMINAL BODY WEIGHT - SUMMARY

DOSAGE GROUP TARGET DOSAGE (MG/KG/DAY)a		1 0 (CARRIER)	2 0.1/50b	3 1.0/100b	4 10.0	5 20.0
RABBITS TESTED	N	5	5	5	5	5
PREGNANT	N	5	5	5	5	5
TERMINAL BODY WEIGHT	MEAN±S.D.	4108.6 ± 352.2	4216.6 ± 311.3	4238.2 ± 275.8	4146.2 ± 268.7	4262.6 ± 329.7
THYROID/PARATHYROID	MEAN±S.D.	0.378 ± 0.107	0.339 ± 0.036	0.373 ± 0.076	0.414 ± 0.127	0.330 ± 0.059
THYROID/PARATHYROID (% TBW)	MEAN±S.D.	0.010 ± 0.0	0.010 ± 0.0	0.010 ± 0.0	0.012 ± 0.004	0.008 ± 0.004

ALL WEIGHTS WERE RECORDED IN GRAMS (G). REL. % TBW = (ORGAN WEIGHT/TERMINAL BODY WEIGHT) x 100.

a. Dosage occurred on days 6 through 28 of gestation.

b. The target dosage levels of Groups 2 and 3 were increased from 0.1 mg/kg/day and 1.0 mg/kg/day to 50 mg/kg/day and 100 mg/kg/day, respectively on day 13 of gestation.

PROTOCOL 1416-002P: ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

TABLE 4 (PAGE 1): MATERNAL BODY WEIGHTS - SUMMARY

DOSAGE GROUP TARGET DOSAGE (MG/KG/DAY)a		1 0 (CARRIER)	2 0.1/50b	3 1.0/100b	4 10.0	5 20.0
RABBITS TESTED	N	5	5	5	5	5
PREGNANT	N	5	5	5	5	5
INCLUDED IN ANALYSES	N	4c	5	5	5	5
MATERNAL BODY WEIGHT (KG)						
DAY 0	MEAN±S.D.	3.64 ± 0.12	3.73 ± 0.31	3.86 ± 0.22	3.80 ± 0.21	3.81 ± 0.26
DAY 6	MEAN±S.D.	3.67 ± 0.11	3.85 ± 0.28	3.80 ± 0.21	3.82 ± 0.20	3.81 ± 0.24
DAY 7	MEAN±S.D.	3.69 ± 0.11	3.81 ± 0.32	3.92 ± 0.22	3.85 ± 0.19	3.87 ± 0.24
DAY 8	MEAN±S.D.	3.71 ± 0.10	3.82 ± 0.32	3.92 ± 0.20	3.87 ± 0.19	3.88 ± 0.20
DAY 9	MEAN±S.D.	3.72 ± 0.11	3.85 ± 0.35	3.96 ± 0.19	3.87 ± 0.21	3.92 ± 0.20
DAY 10	MEAN±S.D.	3.74 ± 0.08	3.86 ± 0.33	3.96 ± 0.21	3.89 ± 0.19	3.92 ± 0.21
DAY 11	MEAN±S.D.	3.76 ± 0.10	3.85 ± 0.32	3.99 ± 0.19	3.90 ± 0.19	3.95 ± 0.21
DAY 12	MEAN±S.D.	3.76 ± 0.05	3.85 ± 0.33	4.03 ± 0.20	3.92 ± 0.21	3.97 ± 0.21
DAY 13	MEAN±S.D.	3.78 ± 0.07	3.89 ± 0.33	4.05 ± 0.18	3.95 ± 0.22	4.01 ± 0.20
DAY 14	MEAN±S.D.	3.78 ± 0.08	3.93 ± 0.31	4.09 ± 0.20	3.98 ± 0.25	4.05 ± 0.23
DAY 15	MEAN±S.D.	3.82 ± 0.08	3.95 ± 0.31	4.13 ± 0.19	3.99 ± 0.25	4.07 ± 0.22
DAY 16	MEAN±S.D.	3.82 ± 0.11	3.96 ± 0.30	4.13 ± 0.20	4.00 ± 0.26	4.09 ± 0.22
DAY 17	MEAN±S.D.	3.80 ± 0.13	3.97 ± 0.32	4.14 ± 0.19	4.01 ± 0.27	4.07 ± 0.22

DAY = DAY OF GESTATION

a. Dosage occurred on days 6 through 28 of gestation.

b. The target dosage levels of Groups 2 and 3 were increased from 0.1 mg/kg/day and 1.0 mg/kg/day to 50 mg/kg/day and 100 mg/kg/day, respectively on day 13 of gestation.

c. Excludes values for doe 6726, which had a unilateral pregnancy and only three live fetuses.

PROTOCOL 1416-002P: ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

TABLE 4 (PAGE 2): MATERNAL BODY WEIGHTS - SUMMARY

DOSAGE GROUP TARGET DOSAGE (MG/KG/DAY)a		1 0 (CARRIER)	2 0.1/50b	3 1.0/100b	4 10.0	5 20.0
RABBITS TESTED	N	5	5	5	5	5
PREGNANT	N	5	5	5	5	5
INCLUDED IN ANALYSES	N	4c	5	5	5	5
MATERNAL BODY WEIGHT (KG)						
DAY 18	MEAN±S.D.	3.83 ± 0.11	4.01 ± 0.33	4.16 ± 0.19	4.01 ± 0.27	4.10 ± 0.21
DAY 19	MEAN±S.D.	3.86 ± 0.11	4.02 ± 0.32	4.19 ± 0.20	4.04 ± 0.29	4.12 ± 0.21
DAY 20	MEAN±S.D.	3.89 ± 0.11	4.04 ± 0.33	4.21 ± 0.18	4.05 ± 0.30	4.15 ± 0.22
DAY 21	MEAN±S.D.	3.90 ± 0.10	4.07 ± 0.32	4.22 ± 0.18	4.07 ± 0.30	4.15 ± 0.21
DAY 22	MEAN±S.D.	3.91 ± 0.10	4.10 ± 0.33	4.28 ± 0.17	4.10 ± 0.34	4.15 ± 0.21
DAY 23	MEAN±S.D.	3.93 ± 0.10	4.13 ± 0.33	4.31 ± 0.17	4.12 ± 0.36	4.16 ± 0.23
DAY 24	MEAN±S.D.	3.94 ± 0.10	4.18 ± 0.34	4.34 ± 0.17	4.12 ± 0.37	4.19 ± 0.24
DAY 25	MEAN±S.D.	3.90 ± 0.16	4.19 ± 0.36	4.35 ± 0.17	4.13 ± 0.38	4.20 ± 0.25
DAY 26	MEAN±S.D.	3.94 ± 0.12	4.17 ± 0.34	4.32 ± 0.22	4.17 ± 0.36	4.24 ± 0.27
DAY 27	MEAN±S.D.	3.92 ± 0.11	4.19 ± 0.33	4.28 ± 0.26	4.16 ± 0.34	4.23 ± 0.30
DAY 28	MEAN±S.D.	3.95 ± 0.12	4.18 ± 0.32	4.24 ± 0.26	4.13 ± 0.30	4.25 ± 0.32
DAY 29	MEAN±S.D.	3.96 ± 0.13	4.22 ± 0.31	4.24 ± 0.27	4.15 ± 0.27	4.26 ± 0.33
GRAVID UTERINE WEIGHT (G)	MEAN±S.D.	455.4 ± 63.4	516.4 ± 72.2	472.0 ± 21.8	500.6 ±103.4	542.5 ±189.5
DAY 29C d	MEAN±S.D.	3.50 ± 0.08	3.70 ± 0.37	3.77 ± 0.26	3.64 ± 0.30	3.72 ± 0.28

DAY = DAY OF GESTATION

a. Dosage occurred on days 6 through 28 of gestation.

b. The target dosage levels of Groups 2 and 3 were increased from 0.1 mg/kg/day and 1.0 mg/kg/day to 50 mg/kg/day and 100 mg/kg/day, respectively on day 13 of gestation.

c. Excludes values for doe 6726, which had a unilateral pregnancy and only three live fetuses.

d. 29C = Corrected maternal body weight (day 29 of gestation body weight minus the gravid uterine weight).

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TABLE 5 (PAGE 1): MATERNAL BODY WEIGHT CHANGES - SUMMARY

DOSAGE GROUP TARGET DOSAGE (MG/KG/DAY)a		1 0 (CARRIER)	2 0.1/50b	3 1.0/100b	4 10.0	5 20.0
RABBITS TESTED	N	5	5	5	5	5
PREGNANT	N	5	5	5	5	5
INCLUDED IN ANALYSES	N	4c	5	5	5	5
MATERNAL BODY WEIGHT CHANGE (KG)						
DAYS 0 - 6	MEAN±S.D.	+0.03 ± 0.02	+0.12 ± 0.07	-0.06 ± 0.08	+0.02 ± 0.10	+0.01 ± 0.11
DAYS 6 - 9	MEAN±S.D.	+0.04 ± 0.07	+0.00 ± 0.09	+0.16 ± 0.06	+0.05 ± 0.06	+0.11 ± 0.06
DAYS 9 - 13	MEAN±S.D.	+0.06 ± 0.05	+0.05 ± 0.03	+0.09 ± 0.03	+0.07 ± 0.03	+0.09 ± 0.02
DAYS 6 - 13	MEAN±S.D.	+0.10 ± 0.08	+0.05 ± 0.08	+0.25 ± 0.07	+0.12 ± 0.09	+0.19 ± 0.08
DAYS 13 - 16	MEAN±S.D.	+0.04 ± 0.04	+0.07 ± 0.08	+0.08 ± 0.02	+0.06 ± 0.05	+0.08 ± 0.03
DAYS 16 - 20	MEAN±S.D.	+0.07 ± 0.05	+0.08 ± 0.04	+0.08 ± 0.02	+0.05 ± 0.04	+0.06 ± 0.04
DAYS 13 - 20	MEAN±S.D.	+0.11 ± 0.06	+0.15 ± 0.08	+0.16 ± 0.02	+0.10 ± 0.09	+0.14 ± 0.04
DAYS 20 - 23	MEAN±S.D.	+0.04 ± 0.01	+0.09 ± 0.01	+0.10 ± 0.02	+0.07 ± 0.06	+0.02 ± 0.04
DAYS 23 - 26	MEAN±S.D.	+0.01 ± 0.06	+0.04 ± 0.02	+0.01 ± 0.11	+0.04 ± 0.05	+0.07 ± 0.06
DAYS 26 - 29	MEAN±S.D.	+0.02 ± 0.05	+0.05 ± 0.08	-0.09 ± 0.11	-0.02 ± 0.11	+0.03 ± 0.07
DAYS 20 - 29	MEAN±S.D.	+0.07 ± 0.10	+0.17 ± 0.07	+0.03 ± 0.20	+0.10 ± 0.05	+0.12 ± 0.15
DAYS 13 - 29	MEAN±S.D.	+0.18 ± 0.13	+0.33 ± 0.08	+0.19 ± 0.18	+0.20 ± 0.07	+0.25 ± 0.16
DAYS 6 - 29	MEAN±S.D.	+0.28 ± 0.14	+0.37 ± 0.10	+0.44 ± 0.18	+0.32 ± 0.12	+0.45 ± 0.16

DAYS = DAYS OF GESTATION

a. Dosage occurred on days 6 through 28 of gestation.
b. The target dosage levels of Groups 2 and 3 were increased from 0.1 mg/kg/day and 1.0 mg/kg/day to 50 mg/kg/day and 100 mg/kg/day, respectively on day 13 of gestation.
c. Excludes values for doe 6726, which had a unilateral pregnancy and only three live fetuses.

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TABLE 5 (PAGE 2): MATERNAL BODY WEIGHT CHANGES - SUMMARY

DOSAGE GROUP TARGET DOSAGE (MG/KG/DAY)a		1 0 (CARRIER)	2 0.1/50b	3 1.0/100b	4 10.0	5 20.0
RABBITS TESTED	N	5	5	5	5	5
PREGNANT	N	5	5	5	5	5
INCLUDED IN ANALYSES	N	4c	5	5	5	5
MATERNAL BODY WEIGHT CHANGE (KG)						
DAYS 0 - 29	MEAN±S.D.	+0.32 ± 0.13	+0.49 ± 0.11	+0.37 ± 0.18	+0.34 ± 0.16	+0.46 ± 0.10
DAYS 6 - 29C d	MEAN±S.D.	-0.17 ± 0.14	-0.15 ± 0.13	-0.04 ± 0.18	-0.18 ± 0.20	-0.09 ± 0.14
DAYS 0 - 29C d	MEAN±S.D.	-0.14 ± 0.14	-0.03 ± 0.12	-0.10 ± 0.18	-0.16 ± 0.25	-0.09 ± 0.20

DAYS = DAYS OF GESTATION

a. Dosage occurred on days 6 through 28 of gestation.

b. The target dosage levels of Groups 2 and 3 were increased from 0.1 mg/kg/day and 1.0 mg/kg/day to 50 mg/kg/day and 100 mg/kg/day, respectively on day 13 of gestation.

c. Excludes values for doe 6726, which had a unilateral pregnancy and only three live fetuses.

d. 29C = Corrected maternal body weight (day 29 of gestation body weight minus the gravid uterine weight).

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TABLE 6 (PAGE 1): MATERNAL ABSOLUTE WATER CONSUMPTION VALUES (G/DAY) - SUMMARY

DOSAGE GROUP TARGET DOSAGE (MG/KG/DAY)a		1 0 (CARRIER)	2 0.1/50b	3 1.0/100b	4 10.0	5 20.0
RABBITS TESTED	N	5	5	5	5	5
PREGNANT	N	5	5	5	5	5
INCLUDED IN ANALYSES	N	4c	5	5	5	5
MATERNAL WATER CONSUMPTION (G/DAY)						
DAYS 2 - 6	MEAN±S.D.	252.7 ± 79.3	256.6 ± 86.3	295.2 ± 33.9	267.2 ± 27.5	315.5 ± 64.2
DAYS 6 - 9	MEAN±S.D.	283.8 ± 90.9	288.3 ±114.9	381.4 ± 47.7	300.5 ± 41.5	377.4 ±111.5
DAYS 9 - 13	MEAN±S.D.	310.9 ±104.4	297.7 ± 66.9	378.9 ± 80.1	309.4 ± 29.0	369.7 ± 74.6
DAYS 6 - 13	MEAN±S.D.	299.3 ± 92.4	293.6 ± 85.9	380.0 ± 64.3	305.6 ± 31.2	373.0 ± 89.8
DAYS 13 - 16	MEAN±S.D.	271.7 ±110.7	352.5 ± 63.3	424.2 ±116.3	291.2 ± 33.1	379.1 ± 81.0
DAYS 16 - 20	MEAN±S.D.	345.5 ± 78.6	378.9 ± 78.1	411.0 ± 83.7	348.9 ± 46.8	380.5 ± 88.6
DAYS 13 - 20	MEAN±S.D.	313.8 ± 88.5	367.6 ± 66.4	416.6 ± 94.0	324.1 ± 26.3	379.9 ± 84.6
DAYS 20 - 23	MEAN±S.D.	309.8 ± 51.1	373.8 ± 80.0	438.1 ±114.2	341.8 ± 49.8	354.4 ± 96.7
DAYS 23 - 26	MEAN±S.D.	313.9 ±115.3	347.5 ± 51.6	283.9 ±106.2	321.1 ± 55.5	338.7 ±118.7
DAYS 26 - 29	MEAN±S.D.	251.4 ±122.9	307.5 ±101.8	178.3 ±110.4	250.3 ±126.9	248.9 ±107.2
DAYS 20 - 29	MEAN±S.D.	288.4 ± 71.7	342.9 ± 61.5	300.1 ±104.3	304.4 ± 71.2	314.0 ±104.3
DAYS 13 - 29	MEAN±S.D.	299.4 ± 66.9	353.7 ± 62.4	351.1 ± 94.6	313.1 ± 44.0	342.8 ± 93.1
DAYS 6 - 29	MEAN±S.D.	299.4 ± 68.0	335.4 ± 68.4	359.9 ± 84.6	310.8 ± 37.9	352.0 ± 88.4
DAYS 2 - 29	MEAN±S.D.	292.4 ± 68.3	323.8 ± 68.5	350.3 ± 72.4	304.3 ± 34.4	346.4 ± 82.4

DAYS = DAYS OF GESTATION

a. Dosage occurred on days 6 through 28 of gestation.

b. The target dosage levels of Groups 2 and 3 were increased from 0.1 mg/kg/day and 1.0 mg/kg/day to 50 mg/kg/day and 100 mg/kg/day, respectively on day 13 of gestation.

c. Excludes values for doe 6726, which had a unilateral pregnancy and only three live fetuses.

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TABLE 7 (PAGE 1): MATERNAL RELATIVE WATER CONSUMPTION VALUES (G/KG/DAY) - SUMMARY

DOSAGE GROUP TARGET DOSAGE (MG/KG/DAY)a		1 0 (CARRIER)	2 0.1/50b	3 1.0/100b	4 10.0	5 20.0
RABBITS TESTED	N	5	5	5	5	5
PREGNANT	N	5	5	5	5	5
INCLUDED IN ANALYSES	N	4c	5	5	5	5
MATERNAL WATER CONSUMPTION (G/KG/DAY)						
DAYS 2 - 6	MEAN±S.D.	69.8 ± 22.6	68.0 ± 23.5	77.2 ± 5.1	71.0 ± 8.6	83.8 ± 17.4
DAYS 6 - 9	MEAN±S.D.	76.9 ± 25.3	75.9 ± 31.1	97.8 ± 12.2	77.9 ± 9.6	97.5 ± 28.4
DAYS 9 - 13	MEAN±S.D.	82.9 ± 27.1	78.1 ± 20.9	94.9 ± 20.4	79.4 ± 7.6	93.5 ± 18.3
DAYS 6 - 13	MEAN±S.D.	80.3 ± 24.6	77.1 ± 24.5	96.2 ± 16.6	78.7 ± 7.4	95.2 ± 22.5
DAYS 13 - 16	MEAN±S.D.	71.6 ± 29.4	90.0 ± 17.1	103.5 ± 29.1	73.2 ± 7.6	93.5 ± 19.4
DAYS 16 - 20	MEAN±S.D.	90.1 ± 20.7	95.8 ± 24.5	98.6 ± 19.1	86.7 ± 9.3	92.5 ± 19.9
DAYS 13 - 20	MEAN±S.D.	82.2 ± 23.1	93.3 ± 20.3	100.7 ± 22.5	80.9 ± 3.8	92.9 ± 19.5
DAYS 20 - 23	MEAN±S.D.	79.4 ± 13.4	92.8 ± 25.6	102.7 ± 25.1	83.9 ± 12.9	85.1 ± 21.4
DAYS 23 - 26	MEAN±S.D.	80.1 ± 29.6	83.9 ± 15.2	65.4 ± 23.3	78.1 ± 15.6	80.4 ± 26.9
DAYS 26 - 29	MEAN±S.D.	64.4 ± 33.3	73.7 ± 24.3	41.2 ± 24.0	61.5 ± 32.0	58.0 ± 22.8
DAYS 20 - 29	MEAN±S.D.	73.8 ± 20.1	83.5 ± 18.0	69.9 ± 22.5	74.5 ± 19.3	74.4 ± 22.8
DAYS 13 - 29	MEAN±S.D.	77.4 ± 18.3	87.7 ± 18.8	83.1 ± 21.2	77.2 ± 12.1	82.4 ± 20.7
DAYS 6 - 29	MEAN±S.D.	78.2 ± 18.3	84.5 ± 20.0	87.0 ± 19.6	77.7 ± 10.1	86.1 ± 20.3
DAYS 2 - 29	MEAN±S.D.	76.8 ± 18.4	81.9 ± 19.6	85.2 ± 16.6	76.4 ± 9.4	85.4 ± 19.1

DAYS = DAYS OF GESTATION

a. Dosage occurred on days 6 through 28 of gestation.

b. The target dosage levels of Groups 2 and 3 were increased from 0.1 mg/kg/day and 1.0 mg/kg/day to 50 mg/kg/day and 100 mg/kg/day, respectively on day 13 of gestation.

c. Excludes values for doe 6726, which had a unilateral pregnancy and only three live fetuses.

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TABLE 8 (PAGE 1): MATERNAL ABSOLUTE FEED CONSUMPTION VALUES (G/DAY) - SUMMARY

DOSAGE GROUP TARGET DOSAGE (MG/KG/DAY)a		1 0 (CARRIER)	2 0.1/50b	3 1.0/100b	4 10.0	5 20.0
RABBITS TESTED	N	5	5	5	5	5
PREGNANT	N	5	5	5	5	5
INCLUDED IN ANALYSES	N	4c	5	5	5	5
MATERNAL FEED CONSUMPTION (G/DAY)						
DAYS 6 - 9	MEAN±S.D.	156.4 ± 31.9	156.1 ± 31.8	181.5 ± 0.9	168.8 ± 21.8	179.1 ± 8.7
DAYS 9 - 13	MEAN±S.D.	150.2 ± 23.2	159.9 ± 20.2	180.9 ± 3.5	165.2 ± 24.9	176.9 ± 11.2
DAYS 6 - 13	MEAN±S.D.	152.8 ± 24.7	158.3 ± 23.0	181.2 ± 1.8	166.8 ± 23.4	177.9 ± 10.0
DAYS 13 - 16	MEAN±S.D.	137.6 ± 40.2	172.1 ± 17.7	181.8 ± 2.3	148.8 ± 41.5	163.5 ± 23.7
DAYS 16 - 20	MEAN±S.D.	151.2 ± 39.8	177.3 ± 7.2	183.1 ± 0.7	167.4 ± 26.2	171.4 ± 20.6
DAYS 13 - 20	MEAN±S.D.	145.4 ± 39.0	175.0 ± 11.6	182.5 ± 0.9	159.4 ± 32.5	168.1 ± 21.3
DAYS 20 - 23	MEAN±S.D.	145.2 ± 8.0	173.9 ± 8.2	183.1 ± 1.2	163.4 ± 24.1	157.1 ± 24.0
DAYS 23 - 26	MEAN±S.D.	101.8 ± 31.0	134.3 ± 25.2	133.7 ± 44.3	133.5 ± 41.8	142.7 ± 37.8
DAYS 26 - 29	MEAN±S.D.	77.6 ± 14.8	114.4 ± 35.4	44.5 ± 53.6	96.9 ± 47.1	125.2 ± 54.2
DAYS 20 - 29	MEAN±S.D.	108.2 ± 15.9	140.9 ± 17.0	120.5 ± 30.0	131.2 ± 27.9	141.7 ± 37.8
DAYS 13 - 29	MEAN±S.D.	124.4 ± 17.7	155.8 ± 10.8	147.6 ± 17.0	143.6 ± 25.3	153.2 ± 27.4
DAYS 6 - 29	MEAN±S.D.	133.1 ± 17.9	156.6 ± 13.7	157.9 ± 12.2	150.6 ± 24.5	160.7 ± 20.8

DAYS = DAYS OF GESTATION

a. Dosage occurred on days 6 through 28 of gestation.

b. The target dosage levels of Groups 2 and 3 were increased from 0.1 mg/kg/day and 1.0 mg/kg/day to 50 mg/kg/day and 100 mg/kg/day, respectively on day 13 of gestation.

c. Excludes values for doe 6726, which had a unilateral pregnancy and only three live fetuses.

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TABLE 9 (PAGE 1): MATERNAL RELATIVE FEED CONSUMPTION VALUES (G/KG/DAY) - SUMMARY

DOSAGE GROUP TARGET DOSAGE (MG/KG/DAY)a		1 0 (CARRIER)	2 0.1/50b	3 1.0/100b	4 10.0	5 20.0
RABBITS TESTED	N	5	5	5	5	5
PREGNANT	N	5	5	5	5	5
INCLUDED IN ANALYSES	N	4c	5	5	5	5
MATERNAL FEED CONSUMPTION (G/KG/DAY)						
DAYS 6 - 9	MEAN±S.D.	42.3 ± 8.6	40.7 ± 7.6	46.6 ± 2.4	43.8 ± 5.1	46.4 ± 4.2
DAYS 9 - 13	MEAN±S.D.	40.1 ± 6.5	41.6 ± 6.1	45.3 ± 2.6	42.2 ± 5.3	44.9 ± 4.4
DAYS 6 - 13	MEAN±S.D.	41.0 ± 6.8	41.2 ± 5.8	45.9 ± 2.5	42.9 ± 5.1	45.6 ± 4.3
DAYS 13 - 16	MEAN±S.D.	36.2 ± 10.4	43.9 ± 5.5	44.4 ± 1.7	37.0 ± 9.0	40.5 ± 6.7
DAYS 16 - 20	MEAN±S.D.	39.2 ± 9.7	44.5 ± 3.1	44.0 ± 2.1	41.5 ± 5.0	41.9 ± 5.9
DAYS 13 - 20	MEAN±S.D.	37.9 ± 9.8	44.2 ± 4.0	44.2 ± 1.9	39.6 ± 6.6	41.3 ± 6.1
DAYS 20 - 23	MEAN±S.D.	37.2 ± 2.4	42.6 ± 1.7	43.1 ± 2.0	39.9 ± 4.9	37.9 ± 5.9
DAYS 23 - 26	MEAN±S.D.	25.9 ± 7.6	32.1 ± 4.3	30.9 ± 10.2	32.3 ± 9.8	33.9 ± 8.2
DAYS 26 - 29	MEAN±S.D.	19.7 ± 4.0	27.4 ± 8.4	10.1 ± 11.7	23.8 ± 12.5	29.1 ± 11.4
DAYS 20 - 29	MEAN±S.D.	27.6 ± 4.0	34.0 ± 3.5	28.1 ± 6.6	32.0 ± 7.5	33.6 ± 8.1
DAYS 13 - 29	MEAN±S.D.	32.0 ± 4.0	38.3 ± 2.5	35.0 ± 4.0	35.3 ± 5.9	36.9 ± 6.2
DAYS 6 - 29	MEAN±S.D.	34.7 ± 4.4	39.2 ± 3.1	38.2 ± 3.2	37.5 ± 5.6	39.5 ± 5.1

DAYS = DAYS OF GESTATION

a. Dosage occurred on days 6 through 28 of gestation.

b. The target dosage levels of Groups 2 and 3 were increased from 0.1 mg/kg/day and 1.0 mg/kg/day to 50 mg/kg/day and 100 mg/kg/day, respectively on day 13 of gestation.

c. Excludes values for doe 6726, which had a unilateral pregnancy and only three live fetuses.

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TABLE 10 (PAGE 1): CAESAREAN-SECTIONING OBSERVATIONS - SUMMARY

DOSAGE GROUP TARGET DOSAGE (MG/KG/DAY)a		1 0 (CARRIER)	2 0.1/50b	3 1.0/100b	4 10.0	5 20.0
RABBITS TESTED	N	5	5	5	5	5
PREGNANT	N(%)	5(100.0)	5(100.0)	5(100.0)	5(100.0)	5(100.0)
RABBITS PREGNANT AND CAESAREAN-SECTIONED ON DAY 29 OF GESTATION	N	5	5	5	5	5
INCLUDED IN ANALYSES	N	4c	5	5	5	5
CORPORA LUTEA	MEAN±S.D.	9.8 ± 3.9	8.2 ± 1.9	9.4 ± 2.2	8.2 ± 1.9	10.2 ± 2.9
IMPLANTATIONS	MEAN±S.D.	7.8 ± 2.2	8.0 ± 1.6	8.0 ± 1.6	7.6 ± 1.7	8.8 ± 2.2
LITTER SIZES	MEAN±S.D.	7.2 ± 1.2	7.6 ± 1.5	8.0 ± 1.6	7.6 ± 1.7	8.2 ± 2.8
LIVE FETUSES	N	29	38	40	38	41
	MEAN±S.D.	7.2 ± 1.2	7.6 ± 1.5	8.0 ± 1.6	7.6 ± 1.7	8.2 ± 2.8
DEAD FETUSES	N	0	0	0	0	0
RESORPTIONS	MEAN±S.D.	0.5 ± 1.0	0.4 ± 0.5	0.0 ± 0.0	0.0 ± 0.0	0.6 ± 1.3
EARLY RESORPTIONS	N	0	0	0	0	3
	MEAN±S.D.	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.6 ± 1.3
LATE RESORPTIONS	N	2	2	0	0	0
	MEAN±S.D.	0.5 ± 1.0	0.4 ± 0.5	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
DOES WITH ANY RESORPTIONS	N(%)	1(25.0)	2(40.0)	0(0.0)	0(0.0)	1(20.0)
DOES WITH ALL CONCEPTUSES RESORBED	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
DOES WITH VIABLE FETUSES	N(%)	4(100.0)	5(100.0)	5(100.0)	5(100.0)	5(100.0)
PLACENTAE APPEARED NORMAL	N(%)	4(100.0)	5(100.0)	5(100.0)	5(100.0)	5(100.0)

a. Dosage occurred on days 6 through 28 of gestation.
b. The target dosage levels of Groups 2 and 3 were increased from 0.1 mg/kg/day and 1.0 mg/kg/day to 50 mg/kg/day and 100 mg/kg/day, respectively on day 13 of gestation.
c. Excludes values for doe 6726, which had a unilateral pregnancy and only three live fetuses.

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TABLE 11 (PAGE 1): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - SUMMARY

DOSAGE GROUP TARGET DOSAGE (MG/KG/DAY)a		1 0 (CARRIER)	2 0.1/50b	3 1.0/100b	4 10.0	5 20.0
LITTERS WITH ONE OR MORE LIVE FETUSES	N	5	5	5	5	5
INCLUDED IN ANALYSES	N	4c	5	5	5	5
IMPLANTATIONS	MEAN±S.D.	7.8 ± 2.2	8.0 ± 1.6	8.0 ± 1.6	7.6 ± 1.7	8.8 ± 2.2
LIVE FETUSES	N	29	38	40	38	41
	MEAN±S.D.	7.2 ± 1.2	7.6 ± 1.5	8.0 ± 1.6	7.6 ± 1.7	8.2 ± 2.8
LIVE MALE FETUSES	N	12	22	26	21	17
% LIVE MALE FETUSES/LITTER	MEAN±S.D.	41.6 ± 20.0	55.0 ± 24.4	66.4 ± 20.1	57.6 ± 24.4	43.5 ± 14.7
LIVE FETAL BODY WEIGHTS (GRAMS)/LITTER	MEAN±S.D.	45.30 ± 2.65	47.10 ± 6.34	42.65 ± 8.02	46.94 ± 2.73	44.18 ± 4.05
MALE FETUSES	MEAN±S.D.	45.84 ± 4.14	48.99 ± 6.28	43.25 ± 8.58	47.51 ± 3.08	44.46 ± 4.72
FEMALE FETUSES	MEAN±S.D.	44.98 ± 2.16	45.04 ± 6.73	41.50 ± 5.98	46.00 ± 2.66	43.61 ± 5.67
% RESORBED CONCEPTUSES/LITTER	MEAN±S.D.	4.6 ± 9.1	4.7 ± 6.5	0.0 ± 0.0	0.0 ± 0.0	7.5 ± 16.8

a. Dosage occurred on days 6 through 28 of gestation.
b. The target dosage levels of Groups 2 and 3 were increased from 0.1 mg/kg/day and 1.0 mg/kg/day to 50 mg/kg/day and 100 mg/kg/day, respectively on day 13 of gestation.
c. Excludes values for doe 6726, which had a unilateral pregnancy and only three live fetuses.

PROTOCOL 1416-002P: ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

TABLE 12 (PAGE 1): FETAL GROSS EXTERNAL ALTERATIONS - SUMMARY
(See footnotes on the last page of this table.)

DOSAGE GROUP		1	2	3	4	5
TARGET DOSAGE (MG/KG/DAY)a		0 (CARRIER)	0.1/50b	1.0/100b	10.0	20.0
LITTERS EVALUATED	N	5	5	5	5	5
FETUSES EVALUATED	N	32	38	40	38	41
LIVE	N	32	38	40	38	41
HEAD: MENINGOCELE						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(20.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(2.4)c
BODY: UMBILICAL HERNIA						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(20.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(2.4)c
TAIL: ABSENT						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(20.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(2.4)c
PALATE: CLEFT						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(20.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(2.4)d
BODY: EDEMA						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(20.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(2.4)d
FORELIMBS: ABSENT						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(20.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(2.4)d
HEAD DISCONNECTED FROM SPINAL COLUMN						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(20.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(2.4)d
ALL THORACIC AND ABDOMINAL VISCERA EXTERNAL						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(20.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(2.4)d
LIVER TO SMALL INTESTINE AND THYMUS: TISSUES ADHERED						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(20.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(2.4)d

PROTOCOL 1416-002P: ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

TABLE 12 (PAGE 2): FETAL GROSS EXTERNAL ALTERATIONS - SUMMARY

DOSAGE GROUP		1	2	3	4	5
TARGET DOSAGE (MG/KG/DAY)a		0 (CARRIER)	0.1/50b	1.0/100b	10.0	20.0
LITTERS EVALUATED	N	5	5	5	5	5
FETUSES EVALUATED	N	32	38	40	38	41
LIVE	N	32	38	40	38	41
ASCITES						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(20.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(2.4)
SPLEEN, RIGHT OVARY AND VENTRAL THORACIC WALL: TISSUES ABSENT						
LITTER INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(20.0)
FETAL INCIDENCE	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(2.4)d

a. Dosage occurred on days 6 through 28 of gestation.
b. The target dosage levels of Groups 2 and 3 were increased from 0.1 mg/kg/day and 1.0 mg/kg/day to 50 mg/kg/day and 100 mg/kg/day, respectively on day 13 of gestation.
c. Fetus 6747-3 had other gross external alterations.
d. Fetus 6748-3 had other gross external alterations.

PROTOCOL 1416-002P: ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

TABLE 13 (PAGE 1): CLINICAL OBSERVATIONS - INDIVIDUAL DATA

RABBIT #		DESCRIPTION
DOSAGE GROUP 1		0 (CARRIER) MG/KG/DAY
6726		NO ADVERSE FINDINGS
6727		NO ADVERSE FINDINGS
6728		NO ADVERSE FINDINGS
6729		NO ADVERSE FINDINGS
6730		NO ADVERSE FINDINGS
DOSAGE GROUP 2		0.1/50 MG/KG/DAY b
6731		NO ADVERSE FINDINGS
6732	DG(27- 29)	LOCALIZED ALOPECIA: UNDERSIDE a
6733	DG(28)	SOFT OR LIQUID FECES
6734		NO ADVERSE FINDINGS
6735		NO ADVERSE FINDINGS
DOSAGE GROUP 3		1.0/100 MG/KG/DAY b
6736		NO ADVERSE FINDINGS
6737	DG(27- 28)	SOFT OR LIQUID FECES
	DG(29)	SCANT FECES
6738		NO ADVERSE FINDINGS
6739	DG(27- 29)	SCANT FECES
6740		NO ADVERSE FINDINGS
DOSAGE GROUP 4		10.0 MG/KG/DAY
6741	DG(29)	SCANT FECES
6742		NO ADVERSE FINDINGS
6743		NO ADVERSE FINDINGS
6744		NO ADVERSE FINDINGS
6745		NO ADVERSE FINDINGS
DOSAGE GROUP 5		20.0 MG/KG/DAY
6746		NO ADVERSE FINDINGS
6747		NO ADVERSE FINDINGS
6748		NO ADVERSE FINDINGS
6749		NO ADVERSE FINDINGS
6750		NO ADVERSE FINDINGS

DG = DAY OF GESTATION

a. Observation confirmed at necropsy.

b. The target dosage levels of Groups 2 and 3 were increased from 0.1 mg/kg/day and 1.0 mg/kg/day to 50 mg/kg/day and 100 mg/kg/day, respectively on day 13 of gestation.

PROTOCOL 1416-002P: ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

TABLE 14 (PAGE 1): NECROPSY OBSERVATIONS - INDIVIDUAL DATA

DOSAGE GROUP TARGET DOSAGE (MG/KG/DAY)	RABBIT NUMBER	DAY OF NECROPSY	PREGNANCY STATUS	DAYS WITH ACCESS TO TEST ARTICLE	OBSERVATIONS a
1 0 (CARRIER)	6726	DG 29	P	23	ALL TISSUES APPEARED NORMAL.
	6727	DG 29	P	23	ALL TISSUES APPEARED NORMAL.
	6728	DG 29	P	23	ALL TISSUES APPEARED NORMAL.
	6729	DG 29	P	23	ALL TISSUES APPEARED NORMAL.
	6730	DG 29	P	23	ALL TISSUES APPEARED NORMAL.
2 0.1/50b	6731	DG 29	P	23	ALL TISSUES APPEARED NORMAL.
	6732	DG 29	P	23	ALL TISSUES APPEARED NORMAL.
	6733	DG 29	P	23	ALL TISSUES APPEARED NORMAL.
	6734	DG 29	P	23	ALL TISSUES APPEARED NORMAL.
	6735	DG 29	P	23	ALL TISSUES APPEARED NORMAL.
3 1.0/100b	6736	DG 29	P	23	ALL TISSUES APPEARED NORMAL.
	6737	DG 29	P	23	ALL TISSUES APPEARED NORMAL.
	6738	DG 29	P	23	ALL TISSUES APPEARED NORMAL.
	6739	DG 29	P	23	ALL TISSUES APPEARED NORMAL.
	6740	DG 29	P	23	ALL TISSUES APPEARED NORMAL.
4 10.0	6741	DG 29	P	23	ALL TISSUES APPEARED NORMAL.
	6742	DG 29	P	23	ALL TISSUES APPEARED NORMAL.
	6743	DG 29	P	23	ALL TISSUES APPEARED NORMAL.
	6744	DG 29	P	23	ALL TISSUES APPEARED NORMAL.
	6745	DG 29	P	23	ALL TISSUES APPEARED NORMAL.
5 20.0	6746	DG 29	P	23	ALL TISSUES APPEARED NORMAL.
	6747	DG 29	P	23	ALL TISSUES APPEARED NORMAL.
	6748	DG 29	P	23	ALL TISSUES APPEARED NORMAL.
	6749	DG 29	P	23	ALL TISSUES APPEARED NORMAL.
	6750	DG 29	P	23	ALL TISSUES APPEARED NORMAL.

P = PREGNANT
DG = DAY OF GESTATION
a. Refer to the individual clinical observations table (Table 13) for external observations confirmed at necropsy.
b. The target dosage levels of Groups 2 and 3 were increased from 0.1 mg/kg/day and 1.0 mg/kg/day to 50 mg/kg/day and 100 mg/kg/day, respectively on day 13 of gestation.

PROTOCOL 1416-002P: ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

TABLE 15 (PAGE 1): TERMINAL BODY WEIGHTS AND THYROID/PARATHYROID WEIGHTS AND RATIOS (%) OF THYROID/PARATHYROID WEIGHT TO TERMINAL BODY WEIGHT - INDIVIDUAL DATA

RABBIT NUMBER	TERMINAL BODY WEIGHT	THYROID/PARATHYROID ABS. WT.	THYROID/PARATHYROID REL. % TBW
DOSAGE GROUP 1			0 (CARRIER) MG/KG/DAY
6726	4704.	0.555	0.01
6727	3897.	0.317	0.01
6728	4101.	0.314	0.01
6729	3806.	0.302	0.01
6730	4035.	0.404	0.01
DOSAGE GROUP 2			0.1/50 MG/KG/DAY a
6731	4619.	0.350	0.01
6732	4209.	0.370	0.01
6733	4229.	0.374	0.01
6734	4280.	0.292	0.01
6735	3746.	0.310	0.01
DOSAGE GROUP 3			1.0/100 MG/KG/DAY a
6736	4713.	0.324	0.01
6737	4015.	0.422	0.01
6738	4226.	0.336	0.01
6739	4130.	0.480	0.01
6740	4107.	0.301	0.01
DOSAGE GROUP 4			10.0 MG/KG/DAY
6741	4513.	0.363	0.01
6742	3814.	0.346	0.01
6743	4286.	0.400	0.01
6744	4127.	0.324	0.01
6745	3991.	0.635	0.02

ALL WEIGHTS WERE RECORDED IN GRAMS (G). ABS. WT. = ORGAN WEIGHT. REL. % TBW = (ORGAN WEIGHT/TERMINAL BODY WEIGHT) x 100.

a. The target dosage levels of Groups 2 and 3 were increased from 0.1 mg/kg/day and 1.0 mg/kg/day to 50 mg/kg/day and 100 mg/kg/day, respectively on day 13 of gestation.

PROTOCOL 1416-002P: ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

TABLE 15 (PAGE 2): TERMINAL BODY WEIGHTS AND THYROID/PARATHYROID WEIGHTS AND RATIOS (%) OF THYROID/PARATHYROID WEIGHT TO TERMINAL BODY WEIGHT - INDIVIDUAL DATA

RABBIT NUMBER	TERMINAL BODY WEIGHT	THYROID/PARATHYROID ABS. WT.	THYROID/PARATHYROID REL. % TBW
DOSAGE GROUP 5		20.0 MG/KG/DAY	
6746	4692.	0.233	0.00
6747	4273.	0.349	0.01
6748	4211.	0.393	0.01
6749	4362.	0.327	0.01
6750	3775.	0.348	0.01

ALL WEIGHTS WERE RECORDED IN GRAMS (G). ABS. WT. = ORGAN WEIGHT. REL. % TBW = (ORGAN WEIGHT/TERMINAL BODY WEIGHT) x 100.

PROTOCOL 1416-002P: ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

TABLE 16 (PAGE 1): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY STATUS	DAY 0	2	5	6	7	8	9	10	11	12	13	14	15
RABBIT #	DOSAGE GROUP 1					0 (CARRIER) MG/KG/DAY							
6726 P a	4.28	4.02	4.22	4.22	4.23	4.23	4.28	4.31	4.31	4.30	4.37	4.40	4.38
6727 P	3.67	3.61	3.69	3.71	3.75	3.77	3.81	3.82	3.88	3.80	3.86	3.87	3.90
6728 P	3.80	3.66	3.81	3.81	3.81	3.82	3.81	3.79	3.82	3.80	3.81	3.82	3.88
6729 P	3.58	3.48	3.64	3.62	3.60	3.61	3.59	3.65	3.66	3.72	3.70	3.72	3.76
6730 P	3.53	3.42	3.56	3.55	3.60	3.65	3.66	3.68	3.70	3.71	3.74	3.71	3.74

	DAY 16	17	18	19	20	21	22	23	24	25	26	27	28
6726 P a	4.45	4.46	4.43	4.48	4.49	4.45	4.47	4.50	4.53	4.58	4.59	4.62	4.66
6727 P	3.93	3.90	3.91	3.95	3.97	4.00	4.00	4.00	3.94	3.90	3.95	3.89	3.88
6728 P	3.88	3.89	3.91	3.92	3.94	3.94	3.96	3.99	4.03	4.04	4.06	4.06	4.09
6729 P	3.69	3.62	3.67	3.70	3.73	3.76	3.78	3.79	3.80	3.67	3.78	3.79	3.82
6730 P	3.78	3.81	3.83	3.86	3.91	3.92	3.89	3.95	3.97	4.00	3.98	3.96	4.02

	DAY 29	GRAVID UTERINE WEIGHT (G)
6726 P a	4.70	267.14
6727 P	3.90	449.60
6728 P	4.10	541.30
6729 P	3.81	388.36
6730 P	4.04	442.30

P = PREGNANT
DAY = DAY OF GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G), ROUNDED TO THREE SIGNIFICANT DIGITS AND REPORTED IN KILOGRAMS (KG).
ALL CALCULATIONS EXCEPT BODY WEIGHT AVERAGES ARE PERFORMED WITH THE UNROUNDED GRAM (G) VALUE.
BODY WEIGHT AVERAGES ARE CALCULATED WITH THE ROUNDED KILOGRAM (KG) VALUE.
a. Doe 6726 had a unilateral pregnancy and only three live fetuses; values excluded from group averages.

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TABLE 16 (PAGE 2): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY STATUS	DAY 0	2	5	6	7	8	9	10	11	12	13	14	15
RABBIT #	DOSAGE GROUP 2						0.1/50 MG/KG/DAY a						
6731 P	4.21	4.10	4.23	4.28	4.30	4.29	4.33	4.31	4.30	4.35	4.37	4.39	4.40
6732 P	3.71	3.64	3.76	3.72	3.77	3.79	3.81	3.82	3.81	3.84	3.88	3.92	3.96
6733 P	3.77	3.66	3.97	3.91	3.80	3.82	3.94	3.97	3.87	3.78	3.93	3.94	3.94
6734 P	3.61	3.65	3.75	3.81	3.80	3.83	3.79	3.82	3.85	3.85	3.83	3.89	3.93
6735 P	3.35	3.33	3.47	3.51	3.40	3.38	3.36	3.40	3.41	3.41	3.45	3.52	3.53

	DAY 16	17	18	19	20	21	22	23	24	25	26	27	28
6731 P	4.40	4.46	4.51	4.51	4.54	4.57	4.62	4.64	4.68	4.73	4.69	4.67	4.63
6732 P	3.98	3.97	3.98	4.00	4.01	4.05	4.08	4.11	4.15	4.15	4.12	4.19	4.17
6733 P	3.89	3.89	3.96	3.94	3.96	3.98	4.01	4.06	4.16	4.12	4.11	4.16	4.18
6734 P	3.98	3.99	4.01	4.04	4.08	4.08	4.11	4.15	4.18	4.20	4.19	4.22	4.21
6735 P	3.57	3.55	3.57	3.60	3.63	3.67	3.69	3.71	3.73	3.73	3.74	3.73	3.72

	DAY 29	GRAVID UTERINE WEIGHT (G)
6731 P	4.62	392.18
6732 P	4.21	545.02
6733 P	4.23	579.05
6734 P	4.28	524.37
6735 P	3.75	541.66

P = PREGNANT
DAY = DAY OF GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G), ROUNDED TO THREE SIGNIFICANT DIGITS AND REPORTED IN KILOGRAMS (KG).
ALL CALCULATIONS EXCEPT BODY WEIGHT AVERAGES ARE PERFORMED WITH THE UNROUNDED GRAM (G) VALUE.
BODY WEIGHT AVERAGES ARE CALCULATED WITH THE ROUNDED KILOGRAM (KG) VALUE.
a. The target dosage levels of Groups 2 and 3 were increased from 0.1 mg/kg/day and 1.0 mg/kg/day to 50 mg/kg/day and 100 mg/kg/day, respectively on day 13 of gestation.

PROTOCOL 1416-002P: ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

TABLE 16 (PAGE 3): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY STATUS	DAY 0	2	5	6	7	8	9	10	11	12	13	14	15
RABBIT #	DOSAGE GROUP 3					1.0/100 MG/KG/DAY a							
6736 P	4.15	4.01	4.19	4.03	4.18	4.16	4.19	4.22	4.20	4.25	4.28	4.33	4.35
6737 P	3.75	3.58	3.76	3.59	3.78	3.81	3.86	3.85	3.90	3.92	3.95	3.98	4.00
6738 P	3.88	3.78	4.04	3.91	3.98	4.02	4.02	4.00	4.04	4.11	4.07	4.12	4.21
6739 P	3.98	3.84	3.94	3.92	4.03	3.99	4.05	4.06	4.12	4.12	4.14	4.21	4.23
6740 P	3.56	3.46	3.59	3.56	3.62	3.63	3.69	3.66	3.71	3.75	3.81	3.82	3.87

	DAY 16	17	18	19	20	21	22	23	24	25	26	27	28
6736 P	4.37	4.35	4.41	4.44	4.42	4.43	4.46	4.50	4.54	4.58	4.67	4.71	4.68
6737 P	4.04	4.03	4.07	4.09	4.13	4.15	4.19	4.23	4.32	4.32	4.22	4.15	4.08
6738 P	4.12	4.22	4.19	4.22	4.22	4.22	4.33	4.32	4.36	4.41	4.36	4.30	4.24
6739 P	4.25	4.22	4.25	4.30	4.32	4.33	4.38	4.43	4.40	4.33	4.28	4.18	4.11
6740 P	3.86	3.87	3.90	3.91	3.94	3.97	4.02	4.06	4.08	4.11	4.08	4.05	4.08

	DAY 29	GRAVID UTERINE WEIGHT (G)
6736 P	4.71	502.81
6737 P	4.02	485.37
6738 P	4.23	456.67
6739 P	4.13	465.73
6740 P	4.11	449.45

P = PREGNANT
DAY = DAY OF GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G), ROUNDED TO THREE SIGNIFICANT DIGITS AND REPORTED IN KILOGRAMS (KG).
ALL CALCULATIONS EXCEPT BODY WEIGHT AVERAGES ARE PERFORMED WITH THE UNROUNDED GRAM (G) VALUE.
BODY WEIGHT AVERAGES ARE CALCULATED WITH THE ROUNDED KILOGRAM (KG) VALUE.
a. The target dosage levels of Groups 2 and 3 were increased from 0.1 mg/kg/day and 1.0 mg/kg/day to 50 mg/kg/day and 100 mg/kg/day, respectively on day 13 of gestation.

PROTOCOL 1416-002P: ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

TABLE 16 (PAGE 4): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY STATUS	DAY 0	2	5	6	7	8	9	10	11	12	13	14	15
RABBIT #	DOSAGE GROUP 4						10.0 MG/KG/DAY						
6741 P	4.04	4.01	4.12	4.15	4.14	4.17	4.19	4.18	4.20	4.24	4.28	4.35	4.35
6742 P	3.68	3.49	3.70	3.68	3.67	3.65	3.63	3.68	3.68	3.66	3.66	3.66	3.68
6743 P	3.86	3.70	3.80	3.80	3.85	3.86	3.89	3.91	3.92	3.94	3.98	4.03	4.04
6744 P	3.92	3.75	3.92	3.84	3.90	3.89	3.89	3.89	3.88	3.91	3.96	3.99	4.03
6745 P	3.51	3.42	3.62	3.64	3.70	3.78	3.75	3.77	3.80	3.83	3.85	3.89	3.86

	DAY 16	17	18	19	20	21	22	23	24	25	26	27	28
6741 P	4.39	4.40	4.41	4.45	4.48	4.50	4.58	4.61	4.65	4.71	4.71	4.67	4.55
6742 P	3.69	3.67	3.69	3.68	3.69	3.74	3.71	3.72	3.73	3.77	3.78	3.79	3.77
6743 P	4.08	4.10	4.09	4.14	4.17	4.18	4.24	4.31	4.30	4.30	4.32	4.30	4.27
6744 P	4.01	4.01	4.01	4.04	4.07	4.10	4.13	4.12	4.10	3.98	4.11	4.10	4.10
6745 P	3.84	3.86	3.85	3.89	3.84	3.84	3.86	3.85	3.84	3.90	3.92	3.94	3.96

	DAY 29	GRAVID UTERINE WEIGHT (G)
6741 P	4.51	488.92
6742 P	3.81	624.10
6743 P	4.29	516.95
6744 P	4.13	533.73
6745 P	3.99	339.18

P = PREGNANT
DAY = DAY OF GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G), ROUNDED TO THREE SIGNIFICANT DIGITS AND REPORTED IN KILOGRAMS (KG).
ALL CALCULATIONS EXCEPT BODY WEIGHT AVERAGES ARE PERFORMED WITH THE UNROUNDED GRAM (G) VALUE.
BODY WEIGHT AVERAGES ARE CALCULATED WITH THE ROUNDED KILOGRAM (KG) VALUE.

PROTOCOL 1416-002P: ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

TABLE 16 (PAGE 5): MATERNAL BODY WEIGHTS - INDIVIDUAL DATA

PREGNANCY STATUS	DAY 0	2	5	6	7	8	9	10	11	12	13	14	15
RABBIT #	DOSAGE GROUP 5					20.0 MG/KG/DAY							
6746 P	4.11	3.87	4.02	4.04	4.07	4.08	4.12	4.12	4.15	4.17	4.20	4.25	4.30
6747 P	3.73	3.70	3.82	3.83	3.87	3.86	3.89	3.88	3.93	3.92	3.96	3.97	4.03
6748 P	3.84	3.77	3.97	3.97	4.02	4.02	4.02	4.05	4.07	4.10	4.10	4.16	4.13
6749 P	3.94	3.80	3.88	3.80	3.91	3.91	3.98	3.97	4.00	4.05	4.11	4.18	4.18
6750 P	3.42	3.26	3.43	3.43	3.47	3.55	3.59	3.58	3.61	3.63	3.68	3.69	3.73

	DAY 16	17	18	19	20	21	22	23	24	25	26	27	28
6746 P	4.28	4.24	4.28	4.28	4.32	4.34	4.38	4.40	4.44	4.47	4.55	4.60	4.67
6747 P	4.02	4.01	4.04	4.12	4.15	4.14	4.14	4.14	4.14	4.17	4.25	4.22	4.25
6748 P	4.15	4.19	4.17	4.15	4.21	4.20	4.17	4.18	4.20	4.20	4.22	4.23	4.20
6749 P	4.24	4.21	4.26	4.28	4.29	4.27	4.26	4.29	4.34	4.36	4.35	4.34	4.34
6750 P	3.74	3.72	3.77	3.76	3.77	3.80	3.81	3.80	3.81	3.80	3.81	3.78	3.78

	DAY 29	GRAVID UTERINE WEIGHT (G)
6746 P	4.69	683.95
6747 P	4.27	334.41
6748 P	4.21	445.35
6749 P	4.36	793.90
6750 P	3.78	455.09

P = PREGNANT
DAY = DAY OF GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G), ROUNDED TO THREE SIGNIFICANT DIGITS AND REPORTED IN KILOGRAMS (KG).
ALL CALCULATIONS EXCEPT BODY WEIGHT AVERAGES ARE PERFORMED WITH THE UNROUNDED GRAM (G) VALUE.
BODY WEIGHT AVERAGES ARE CALCULATED WITH THE ROUNDED KILOGRAM (KG) VALUE.

PROTOCOL 1416-002P: ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

TABLE 17 (PAGE 1): MATERNAL WATER CONSUMPTION VALUES - INDIVIDUAL DATA

PREGNANCY STATUS DAYS	2 - 3	3 - 4	4 - 5	5 - 6	6 - 7	7 - 8	8 - 9	9 - 10	10 - 11	11 - 12	12 - 13	13 - 14	14 - 15
RABBIT #	DOSAGE GROUP 1						0 (CARRIER) MG/KG/DAY						
6726 P a	240.	939.	319.	368.	423.	317.	315.	326.	334.	378.	310.	429.	265.
6727 P	236.	397.	340.	349.	380.	295.	343.	399.	434.	277.	642.	340.	151.
6728 P	212.	163.	205.	101.	212.	205.	210.	162.	173.	204.	215.	93.	238.
6729 P	163.	210.	242.	186.	188.	229.	196.	296.	262.	325.	239.	243.	181.
6730 P	296.	373.	284.	286.	435.	377.	336.	381.	302.	355.	308.	373.	381.

PREGNANCY STATUS DAYS	15 - 16	16 - 17	17 - 18	18 - 19	19 - 20	20 - 21	21 - 22	22 - 23	23 - 24	24 - 25	25 - 26	26 - 27	27 - 28
6726 P a	454.	359.	450.	355.	437.	339.	266.	336.	523.	282.	362.	338.	393.
6727 P	493.	324.	541.	446.	296.	398.	323.	378.	235.	183.	170.	182.	224.
6728 P	148.	225.	253.	219.	233.	229.	b	327.	266.	b	241.	168.	146.
6729 P	178.	206.	398.	410.	392.	323.	315.	377.	478.	39.	522.	349.	422.
6730 P	441.	396.	380.	424.	385.	335.	112.	323.	442.	482.	455.	150.	287.

PREGNANCY STATUS DAYS	28 - 29
6726 P a	304.
6727 P	187.
6728 P	75.
6729 P	481.
6730 P	345.

P = PREGNANT
DAYS = DAYS OF GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).
a. Doe 6726 had a unilateral pregnancy and only three live fetuses; values excluded from group averages.
b. Spilled water precluded the calculation of this value.

PROTOCOL 1416-002P: ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

TABLE 17 (PAGE 2): MATERNAL WATER CONSUMPTION VALUES - INDIVIDUAL DATA

PREGNANCY STATUS DAYS	2 - 3	3 - 4	4 - 5	5 - 6	6 - 7	7 - 8	8 - 9	9 - 10	10 - 11	11 - 12	12 - 13	13 - 14	14 - 15
RABBIT #	DOSAGE GROUP 2					0.1/50 MG/KG/DAY a							
6731 P	239.	215.	195.	252.	236.	216.	251.	185.	227.	309.	318.	304.	327.
6732 P	279.	205.	261.	216.	320.	310.	279.	278.	273.	318.	335.	460.	316.
6733 P	265.	138.	216.	217.	187.	190.	133.	209.	275.	189.	177.	300.	266.
6734 P	329.	344.	404.	557.	561.	454.	410.	304.	349.	437.	468.	450.	451.
6735 P	150.	213.	200.	237.	250.	276.	252.	317.	296.	355.	334.	328.	280.

PREGNANCY STATUS DAYS	15 - 16	16 - 17	17 - 18	18 - 19	19 - 20	20 - 21	21 - 22	22 - 23	23 - 24	24 - 25	25 - 26	26 - 27	27 - 28
6731 P	389.	324.	292.	357.	320.	295.	326.	231.	443.	358.	235.	168.	207.
6732 P	386.	375.	427.	451.	420.	408.	399.	449.	435.	382.	225.	401.	340.
6733 P	246.	263.	243.	273.	302.	318.	277.	292.	298.	207.	291.	289.	317.
6734 P	413.	402.	393.	399.	538.	513.	334.	368.	399.	373.	435.	464.	449.
6735 P	372.	470.	412.	368.	549.	511.	487.	399.	479.	350.	303.	272.	212.

PREGNANCY STATUS DAYS	28 - 29
6731 P	222.
6732 P	353.
6733 P	269.
6734 P	438.
6735 P	211.

P = PREGNANT
DAYS = DAYS OF GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).
a. The target dosage levels of Groups 2 and 3 were increased from 0.1 mg/kg/day and 1.0 mg/kg/day to 50 mg/kg/day and 100 mg/kg/day, respectively on day 13 of gestation.

PROTOCOL 1416-002P: ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

TABLE 17 (PAGE 3): MATERNAL WATER CONSUMPTION VALUES - INDIVIDUAL DATA

PREGNANCY STATUS DAYS	2 - 3	3 - 4	4 - 5	5 - 6	6 - 7	7 - 8	8 - 9	9 - 10	10 - 11	11 - 12	12 - 13	13 - 14	14 - 15
RABBIT #	DOSAGE GROUP 3					1.0/100 MG/KG/DAY a							
6736 P	354.	296.	329.	337.	477.	406.	364.	417.	512.	403.	437.	530.	386.
6737 P	191.	285.	410.	210.	403.	489.	441.	525.	469.	489.	436.	677.	540.
6738 P	251.	341.	347.	240.	438.	306.	342.	311.	364.	383.	320.	403.	305.
6739 P	335.	259.	325.	390.	406.	322.	350.	342.	259.	242.	290.	332.	339.
6740 P	211.	278.	277.	237.	315.	348.	314.	342.	341.	396.	301.	335.	311.

PREGNANCY STATUS DAYS	15 - 16	16 - 17	17 - 18	18 - 19	19 - 20	20 - 21	21 - 22	22 - 23	23 - 24	24 - 25	25 - 26	26 - 27	27 - 28
6736 P	490.	502.	472.	508.	541.	605.	566.	567.	456.	410.	401.	383.	371.
6737 P	610.	566.	531.	428.	459.	496.	651.	483.	440.	349.	152.	113.	54.
6738 P	369.	353.	334.	317.	294.	408.	339.	391.	314.	294.	187.	128.	82.
6739 P	391.	401.	360.	312.	384.	332.	378.	333.	235.	85.	61.	24.	7.
6740 P	345.	380.	332.	417.	329.	363.	329.	330.	332.	309.	234.	178.	160.

PREGNANCY STATUS DAYS	28 - 29
6736 P	222.
6737 P	509.
6738 P	94.
6739 P	94.
6740 P	256.

P = PREGNANT
DAYS = DAYS OF GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).
a. The target dosage levels of Groups 2 and 3 were increased from 0.1 mg/kg/day and 1.0 mg/kg/day to 50 mg/kg/day and 100 mg/kg/day, respectively on day 13 of gestation.

PROTOCOL 1416-002P: ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

TABLE 17 (PAGE 4): MATERNAL WATER CONSUMPTION VALUES - INDIVIDUAL DATA

PREGNANCY STATUS DAYS	2 - 3	3 - 4	4 - 5	5 - 6	6 - 7	7 - 8	8 - 9	9 - 10	10 - 11	11 - 12	12 - 13	13 - 14	14 - 15
RABBIT #	DOSAGE GROUP 4					10.0 MG/KG/DAY							
6741 P	265.	221.	219.	229.	370.	280.	282.	315.	282.	303.	287.	358.	303.
6742 P	258.	a	284.	257.	259.	255.	215.	324.	244.	256.	233.	440.	178.
6743 P	295.	266.	320.	311.	347.	376.	351.	338.	327.	341.	290.	151.	327.
6744 P	212.	322.	265.	364.	327.	260.	323.	313.	325.	351.	343.	257.	280.
6745 P	228.	288.	217.	257.	280.	301.	282.	297.	348.	327.	344.	340.	332.

PREGNANCY STATUS DAYS	15 - 16	16 - 17	17 - 18	18 - 19	19 - 20	20 - 21	21 - 22	22 - 23	23 - 24	24 - 25	25 - 26	26 - 27	27 - 28
6741 P	323.	348.	377.	405.	272.	267.	285.	351.	346.	298.	262.	178.	27.
6742 P	190.	262.	287.	296.	309.	330.	235.	263.	268.	260.	253.	240.	204.
6743 P	336.	398.	404.	405.	407.	417.	348.	375.	312.	304.	243.	188.	267.
6744 P	246.	390.	362.	403.	379.	421.	359.	373.	465.	11.	706.	469.	476.
6745 P	307.	293.	298.	381.	302.	335.	362.	406.	368.	358.	363.	388.	331.

PREGNANCY STATUS DAYS	28 - 29
6741 P	52.
6742 P	164.
6743 P	199.
6744 P	310.
6745 P	261.

P = PREGNANT
DAYS = DAYS OF GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).
a. Spilled water precluded the calculation of this value.

PROTOCOL 1416-002P: ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

TABLE 17 (PAGE 5): MATERNAL WATER CONSUMPTION VALUES - INDIVIDUAL DATA

PREGNANCY STATUS DAYS	2 - 3	3 - 4	4 - 5	5 - 6	6 - 7	7 - 8	8 - 9	9 - 10	10 - 11	11 - 12	12 - 13	13 - 14	14 - 15
RABBIT #	DOSAGE GROUP 5					20.0 MG/KG/DAY							
6746 P	383.	315.	310.	335.	403.	343.	370.	337.	378.	401.	405.	488.	357.
6747 P	338.	412.	478.	404.	616.	498.	527.	430.	450.	514.	464.	423.	480.
6748 P	344.	283.	292.	272.	334.	160.	298.	302.	261.	304.	285.	326.	259.
6749 P	131.	79.	352.	363.	461.	374.	396.	478.	392.	414.	371.	395.	366.
6750 P	341.	212.	a	361.	339.	249.	293.	296.	312.	306.	295.	326.	299.

PREGNANCY STATUS DAYS	15 - 16	16 - 17	17 - 18	18 - 19	19 - 20	20 - 21	21 - 22	22 - 23	23 - 24	24 - 25	25 - 26	26 - 27	27 - 28
6746 P	459.	494.	435.	460.	463.	534.	398.	420.	410.	454.	379.	393.	439.
6747 P	550.	540.	467.	471.	377.	385.	439.	554.	606.	456.	459.	398.	450.
6748 P	276.	277.	248.	272.	283.	230.	225.	291.	300.	336.	255.	224.	220.
6749 P	349.	450.	390.	397.	351.	289.	365.	346.	287.	252.	190.	164.	174.
6750 P	334.	297.	310.	330.	298.	306.	251.	283.	295.	231.	170.	179.	165.

PREGNANCY STATUS DAYS	28 - 29
6746 P	246.
6747 P	265.
6748 P	138.
6749 P	134.
6750 P	144.

P = PREGNANT
DAYS = DAYS OF GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).
a. Spilled water precluded the calculation of this value.

PROTOCOL 1416-002P: ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

TABLE 18 (PAGE 1): MATERNAL FEED CONSUMPTION VALUES - INDIVIDUAL DATA

PREGNANCY STATUS	DAYS 6 - 9	9 - 13	13 - 16	16 - 19	19 - 21	21 - 24	24 - 27	27 - 29
RABBIT #	DOSAGE GROUP 1					0 (CARRIER) MG/KG/DAY		
6726 P a	546.	735.	551.	552.	364.	543.	548.	365.
6727 P	546.	640.	510.	516.	317.	307.	178.	118.
6728 P	437.	487.	376.	502.	315.	422.	325.	158.
6729 P	348.	572.	258.	222.	295.	415.	242.	193.
6730 P	546.	704.	507.	549.	342.	433.	294.	171.
	DOSAGE GROUP 2					0.1/50 MG/KG/DAY b		
6731 P	510.	687.	548.	551.	367.	550.	405.	127.
6732 P	550.	622.	529.	546.	349.	520.	303.	279.
6733 P	360.	515.	423.	495.	348.	493.	383.	274.
6734 P	551.	729.	551.	545.	364.	515.	458.	289.
6735 P	371.	646.	530.	530.	336.	451.	267.	140.
	DOSAGE GROUP 3					1.0/100 MG/KG/DAY b		
6736 P	547.	728.	555.	549.	365.	549.	485.	230.
6737 P	542.	727.	547.	553.	365.	545.	203.	4.
6738 P	542.	734.	547.	546.	364.	545.	269.	4.
6739 P	548.	699.	542.	551.	364.	508.	51.	31.
6740 P	544.	730.	536.	550.	370.	544.	366.	173.
	DOSAGE GROUP 4					10.0 MG/KG/DAY		
6741 P	548.	728.	549.	548.	337.	552.	446.	26.
6742 P	402.	489.	232.	347.	286.	329.	302.	147.
6743 P	551.	697.	513.	548.	363.	492.	301.	160.
6744 P	481.	665.	473.	547.	370.	414.	255.	212.
6745 P	550.	726.	465.	505.	345.	539.	538.	345.

P = PREGNANT
DAYS = DAYS OF GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).
a. Doe 6726 had a unilateral pregnancy and only three live fetuses; values excluded from group averages.
b. The target dosage levels of Groups 2 and 3 were increased from 0.1 mg/kg/day and 1.0 mg/kg/day to 50 mg/kg/day and 100 mg/kg/day, respectively on day 13 of gestation.

PROTOCOL 1416-002P: ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

TABLE 18 (PAGE 2): MATERNAL FEED CONSUMPTION VALUES - INDIVIDUAL DATA

PREGNANCY STATUS	DAYS 6 - 9	9 - 13	13 - 16	16 - 19	19 - 21	21 - 24	24 - 27	27 - 29
RABBIT #	DOSAGE GROUP 5					20.0 MG/KG/DAY		
6746 P	546.	729.	552.	547.	363.	551.	551.	364.
6747 P	545.	732.	546.	547.	366.	542.	549.	367.
6748 P	491.	629.	385.	410.	263.	424.	350.	196.
6749 P	553.	715.	452.	545.	284.	398.	271.	166.
6750 P	552.	734.	518.	551.	343.	435.	280.	142.

P = PREGNANT
DAYS = DAYS OF GESTATION
ALL WEIGHTS WERE RECORDED IN GRAMS (G).

PROTOCOL 1416-002P: ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

TABLE 19 (PAGE 1): CAESAREAN-SECTIONING OBSERVATIONS - INDIVIDUAL DATA

			VIABLE FETUSES			DEAD FETUSES		EARLY RESORPTIONS		LATE RESORPTIONS		IMPLANTATION SITES		CORPORA LUTEA	
	SEX		RIGHT	LEFT		RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT
RABBIT #	M	F	HORN	HORN	TOTAL	HORN	TOTAL	HORN	TOTAL	HORN	TOTAL	HORN	TOTAL	OVARY	TOTAL
DOSAGE GROUP 1							0 (CARRIER) MG/KG/DAY								
6726a	0	3	0	3	3	0	0	0	0	0	0	0	3	3	0	4	4
6727	2	5	3	4	7	0	0	0	0	0	0	3	4	7	4	6	10
6728	3	6	6	3	9	0	0	0	0	1	1	7	4	11	8	7	15
6729	2	4	4	2	6	0	0	0	0	0	0	4	2	6	4	2	6
6730	5	2	4	3	7	0	0	0	0	0	0	4	3	7	4	4	8
DOSAGE GROUP 2							0.1/50 MG/KG/DAY b								
6731	1	5	1	5	6	0	0	0	0	0	0	1	5	6	1	5	6
6732	5	2	2	5	7	0	0	0	0	0	1	2	6	8	2	6	8
6733	8	2	5	5	10	0	0	0	0	0	0	5	5	10	6	5	11
6734	4	4	4	4	8	0	0	0	0	0	1	4	5	9	4	5	9
6735	4	3	5	2	7	0	0	0	0	0	0	5	2	7	5	2	7
DOSAGE GROUP 3							1.0/100 MG/KG/DAY b								
6736	6	1	4	3	7	0	0	0	0	0	0	4	3	7	5	5	10
6737	5	4	7	2	9	0	0	0	0	0	0	7	2	9	7	2	9
6738	7	3	6	4	10	0	0	0	0	0	0	6	4	10	6	4	10
6739	3	5	4	4	8	0	0	0	0	0	0	4	4	8	5	7	12
6740	5	1	3	3	6	0	0	0	0	0	0	3	3	6	3	3	6
DOSAGE GROUP 4							10.0 MG/KG/DAY								
6741	3	4	3	4	7	0	0	0	0	0	0	3	4	7	4	4	8
6742	3	6	9	0	9	0	0	0	0	0	0	9	0	9	9	0	9
6743	7	1	3	5	8	0	0	0	0	0	0	3	5	8	4	6	10
6744	4	5	4	5	9	0	0	0	0	0	0	4	5	9	4	5	9
6745	4	1	3	2	5	0	0	0	0	0	0	3	2	5	3	2	5

M = MALE F = FEMALE

PLACENTAE APPEARED NORMAL UNLESS NOTED OTHERWISE.

a. Doe 6726 had a unilateral pregnancy and only three live fetuses; values excluded from group averages.

b. The target dosage levels of Groups 2 and 3 were increased from 0.1 mg/kg/day and 1.0 mg/kg/day to 50 mg/kg/day and 100 mg/kg/day, respectively on day 13 of gestation.

PROTOCOL 1416-002P: ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

TABLE 19 (PAGE 2): CAESAREAN-SECTIONING OBSERVATIONS - INDIVIDUAL DATA

DOSAGE GROUP 5 — 20.0 MG/KG/DAY

			VIABLE FETUSES			DEAD FETUSES			EARLY RESORPTIONS			LATE RESORPTIONS			IMPLANTATION SITES			CORPORA LUTEA		
	SEX		RIGHT	LEFT		RIGHT	LEFT		RIGHT	LEFT		RIGHT	LEFT		RIGHT	LEFT		RIGHT	LEFT	
RABBIT #	M	F	HORN		TOTAL	HORN		TOTAL	HORN		TOTAL	HORN		TOTAL	HORN		TOTAL	OVARY		TOTAL
6746	3	7	6	4	10	0	0	0	0	0	0	0	0	0	6	4	10	6	4	10
6747	3	2	3	2	5	0	0	0	2	1	3	0	0	0	5	3	8	6	8	14
6748	4	3	4	3	7	0	0	0	0	0	0	0	0	0	4	3	7	4	4	8
6749	5	7	6	6	12	0	0	0	0	0	0	0	0	0	6	6	12	6	6	12
6750	2	5	2	5	7	0	0	0	0	0	0	0	0	0	2	5	7	2	5	7

M = MALE F = FEMALE
PLACENTAE APPEARED NORMAL UNLESS NOTED OTHERWISE.

PROTOCOL 1416-002P: ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

TABLE 20 (PAGE 1): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - INDIVIDUAL DATA

	NUMBER OF LIVE FETUSES			AVERAGE FETAL BODY WEIGHT (G)			---- CONCEPTUSES ------ RESORBED		
RABBIT #	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL a	N	N	%
DOSAGE GROUP 1				0 (CARRIER) MG/KG/DAY					
6726b	0	3	3	----	58.49	58.49	3	0	0.0
6727	2	5	7	47.97	43.24	44.59	7	0	0.0
6728	3	6	9	39.77	43.50	42.26	11	2	18.2
6729	2	4	6	46.72	45.25	45.74	6	0	0.0
6730	5	2	7	48.90	47.94	48.63	7	0	0.0
DOSAGE GROUP 2				0.1/50 MG/KG/DAY c					
6731	1	5	6	49.57	43.32	44.36	6	0	0.0
6732	5	2	7	52.48	48.56	51.36	8	1	12.5
6733	8	2	10	40.95	36.02	39.96	10	0	0.0
6734	4	4	8	44.93	43.22	44.08	9	1	11.1
6735	4	3	7	57.01	54.06	55.75	7	0	0.0
DOSAGE GROUP 3				1.0/100 MG/KG/DAY c					
6736	6	1	7	47.09	45.49	46.86	7	0	0.0
6737	5	4	9	37.68	38.48	38.04	9	0	0.0
6738	7	3	10	32.31	34.04	32.82	10	0	0.0
6739	3	5	8	44.66	40.21	41.88	8	0	0.0
6740	5	1	6	54.51	49.29	53.64	6	0	0.0
DOSAGE GROUP 4				10.0 MG/KG/DAY					
6741	3	4	7	50.64	47.47	48.83	7	0	0.0
6742	3	6	9	49.66	49.27	49.40	9	0	0.0
6743	7	1	8	46.56	44.54	46.30	8	0	0.0
6744	4	5	9	42.77	42.38	42.55	9	0	0.0
6745	4	1	5	47.91	46.35	47.60	5	0	0.0

a. TOTAL = SUM OF FETAL WEIGHTS/NUMBER OF LIVE FETUSES.
b. Doe 6726 had a unilateral pregnancy and only three live fetuses; values excluded from group averages.
c. The target dosage levels of Groups 2 and 3 were increased from 0.1 mg/kg/day and 1.0 mg/kg/day to 50 mg/kg/day and 100 mg/kg/day, respectively on day 13 of gestation.

PROTOCOL 1416-002P: ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

TABLE 20 (PAGE 2): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - INDIVIDUAL DATA

DOSAGE GROUP 5				20.0 MG/KG/DAY					
	NUMBER OF LIVE FETUSES			AVERAGE FETAL BODY WEIGHT (G)			---- CONCEPTUSES ------		
								RESORBED	
RABBIT #	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL a	N	N	%
6746	3	7	10	45.31	48.63	47.63	10	0	0.0
6747	3	2	5	36.31	42.56	38.81	8	3	37.5
6748	4	3	7	45.77	34.28	40.85	7	0	0.0
6749	5	7	12	48.47	45.56	46.77	12	0	0.0
6750	2	5	7	46.46	47.02	46.86	7	0	0.0

a. TOTAL = SUM OF FETAL WEIGHTS/NUMBER OF LIVE FETUSES.

PROTOCOL 1416-002P: ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

TABLE 21 (PAGE 1): FETAL SEX, VITAL STATUS AND BODY WEIGHT - INDIVIDUAL DATA

FETUS #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
DOSAGE GROUP 1							0 (CARRIER) MG/KG/DAY												
RABBIT # CLs																			
6726a 0/ 4 /	FA	FA	FA																
	55.93	59.35	60.20																
6727 4/ 6	MA	FA	FA /	FA	FA	FA	MA												
	51.29	44.91	36.54	44.35	44.81	45.60	44.65												
6728 8/ 7	FA	FA	FA	L	MA	MA	FA /	FA	L	MA	FA								
	41.03	42.80	41.90		39.23	36.30	42.42	49.37		43.79	43.48								
6729 4/ 2	MA	FA	FA	MA /	FA	FA													
	51.78	46.01	41.19	41.66	46.54	47.25													
6730 4/ 4	MA	MA	MA	FA /	MA	MA	FA												
	51.04	48.68	50.00	49.21	45.10	49.68	46.68												
DOSAGE GROUP 2							0.1/50 MG/KG/DAY b												
CLs																			
6731 1/ 5	MA /	FA	FA	FA	FA	FA													
	49.57	50.77	48.15	39.94	39.40	38.35													
6732 2/ 6	MA	MA /	MA	MA	MA	L	FA	FA											
	55.56	53.68	54.43	50.63	48.11	23.69	45.27	51.86											
6733 6/ 5	MA	FA	MA	MA	MA /	MA	MA	MA	FA	MA									
	45.15	41.51	35.60	42.01	36.74	43.40	41.63	43.18	30.52	39.88									
6734 4/ 5	FA	MA	MA	FA /	FA	MA	L	MA	FA										
	44.97	47.97	47.10	44.31	49.34	48.04		36.61	34.26										
6735 5/ 2	MA	MA	FA	FA	FA /	MA	MA												
	53.91	60.13	53.25	56.82	52.12	57.72	56.28												

M = MALE F = FEMALE A = ALIVE E = EARLY RESORPTION L = LATE RESORPTION "/" DENOTES POSITION OF CERVIX
CLs = CORPORA LUTEA/OVARY FETAL BODY WEIGHTS WERE RECORDED IN GRAMS (G).

a. Doe 6726 had a unilateral pregnancy and only three live fetuses; values excluded from group averages.
b. The target dosage levels of Groups 2 and 3 were increased from 0.1 mg/kg/day and 1.0 mg/kg/day to 50 mg/kg/day and 100 mg/kg/day, respectively on day 13 of gestation.

PROTOCOL 1416-002P: ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

TABLE 21 (PAGE 2): FETAL SEX, VITAL STATUS AND BODY WEIGHT - INDIVIDUAL DATA

FETUS #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
DOSAGE GROUP 3							1.0/100 MG/KG/DAY a												
RABBIT # CLs																			
6736 5/ 5	MA	MA	MA	MA /	FA	MA	MA												
	51.93	49.35	45.17	44.92	45.49	46.03	45.13												
6737 7/ 2	FA	MA	FA	FA	MA	MA	FA /	MA	MA										
	44.46	41.62	40.87	36.30	35.59	27.41	32.31	45.88	37.88										
6738 6/ 4	FA	MA	MA	MA	FA	MA /	MA	FA	MA	MA									
	41.41	33.87	31.21	30.65	27.80	31.42	40.64	32.90	25.09	33.27									
6739 5/ 7	MA	MA	FA	FA /	FA	MA	FA	FA											
	41.60	43.11	37.74	36.55	44.24	49.28	42.14	40.39											
6740 3/ 3	MA	MA	FA /	MA	MA	MA													
	57.02	56.62	49.29	55.57	54.95	48.37													
DOSAGE GROUP 4							10.0 MG/KG/DAY												
CLs																			
6741 4/ 4	MA	FA	FA /	FA	MA	FA	MA												
	52.13	46.72	48.82	47.69	48.55	46.65	51.23												
6742 9/ 0	FA	MA	FA	FA	MA	FA	MA	FA	FA /										
	50.77	50.96	48.21	50.58	51.21	45.59	46.80	50.30	50.15										
6743 4/ 6	MA	MA	MA /	MA	FA	MA	MA	MA											
	51.26	45.61	47.97	49.99	44.54	45.05	37.66	48.36											
6744 4/ 5	MA	MA	FA	FA /	FA	FA	MA	FA	MA										
	40.93	44.13	42.45	44.62	43.48	39.47	40.39	41.88	45.62										
6745 3/ 2	MA	MA	FA /	MA	MA														
	48.09	46.13	46.35	46.54	50.90														

M = MALE F = FEMALE A = ALIVE E = EARLY RESORPTION L = LATE RESORPTION "/" DENOTES POSITION OF CERVIX
CLs = CORPORA LUTEA/OVARY FETAL BODY WEIGHTS WERE RECORDED IN GRAMS (G).
a. The target dosage levels of Groups 2 and 3 were increased from 0.1 mg/kg/day and 1.0 mg/kg/day to 50 mg/kg/day and 100 mg/kg/day, respectively on day 13 of gestation.

PROTOCOL 1416-002P: ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

TABLE 21 (PAGE 3): FETAL SEX, VITAL STATUS AND BODY WEIGHT - INDIVIDUAL DATA

FETUS #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
DOSAGE GROUP 5							20.0 MG/KG/DAY												
RABBIT # CLs																			
6746 6/ 4	FA	FA	FA	MA	FA	MA /	FA	FA	MA	FA									
	47.21	52.24	48.82	51.47	43.40	31.89	51.10	49.09	52.56	48.54									
6747a 6/ 8	MA	E	MA	MA	E /	FA	E	FA											
	42.69		15.23	51.02		36.45		48.66											
6748b 4/ 4	MA	FA	FA	MA /	MA	FA	MA												
	42.94	42.42	19.98	48.49	48.97	40.44	42.70												
6749c 6/ 6	MA	FA	MA	MA	FA	FA /	MA	FA	MA	FA	FA	FA							
	50.58	49.16	51.24	43.97	38.58	48.36	49.34	49.22	47.22	45.57	41.32	46.71							
6750 2/ 5	FA	MA /	FA	FA	FA	MA	FA												
	47.57	45.21	54.45	48.08	45.83	47.71	39.19												

M = MALE F = FEMALE A = ALIVE E = EARLY RESORPTION L = LATE RESORPTION "/" DENOTES POSITION OF CERVIX
CLs = CORPORA LUTEA/OVARY FETAL BODY WEIGHTS WERE RECORDED IN GRAMS (G).

a. Fetus 6747-3 had a meningocele, an umbilical hernia, and an absent tail.
b. Fetus 6748-3 had a cleft palate, an edematous body, the head disconnected from the spinal column, all thoracic and abdominal viscera external, liver adhered to small intestines and thymus, and no spleen, right ovary, ventral thoracic wall or forelimbs.
c. Fetus 6749-1 had ascites.

ATTACHMENT 1

PROTOCOL AND AMENDMENTS

Argus Research Laboratories, Inc.
905 Sheehy Drive, Building A
Horsham, Pennsylvania 19044
T: (215) 443-8710 F: (215) 443-8587

PROTOCOL 1416-002P

STUDY TITLE: Oral (Drinking Water) Dosage-Range Developmental Toxicity Study of Ammonium Perchlorate in Rabbits

PURPOSE: The purpose of this study is to provide information for the selection of dosages to be used in the developmental toxicity (embryo-fetal toxicity and teratogenic potential) study of Ammonium Perchlorate administered orally via drinking water to New Zealand White [Hra:(NZW)SPF] presumed pregnant female rabbits.

TESTING FACILITY: Argus Research Laboratories, Inc.
905 Sheehy Drive, Building A
Horsham, Pennsylvania 19044-1297
Telephone: (215) 443-8710
Telefax: (215) 443-8587

STUDY DIRECTOR: Raymond G. York , Ph.D., DABT
Associate Director of Research

SPONSOR: Perchlorate Study Group
Highway 50 & Aerojet Road
Building 20019/Department 0330
Sacramento, California 95670

STUDY MONITOR: Michael F. Girard
Perchlorate Study Group Representative
Telephone: (916) 355-2945
Telefax: (916) 355-6145

SCIENTIFIC ADVISOR: Michael L. Dourson, Ph.D., DABT
Toxicology Excellence for Risk Assessment (TERA)
4303 Kirby Avenue
Cincinnati, Ohio 45223
Telephone: (513) 542-7475
Telefax: (513) 542-7487

REGULATORY CITATIONS:

U.S. Environmental Protection Agency (1996). Health Effects Test Guidelines; Prenatal Developmental Toxicity Study. Prevention, Pesticides and Toxic Substances (OPPTS) 870.3700, February 1996.

U.S. Environmental Protection Agency (1984). *Pesticide Assessment Guidelines.* Subdivision F - Hazard Evaluation: Human and Domestic Animals, November, 1984 (Revised Edition).

Organization for Economic Cooperation and Development (1981). *Guidelines for Testing of Chemicals*. Section 4, No. 414: Teratogenicity, pp. 1-6.

Japanese Ministry of Agriculture, Forestry and Fisheries (1985). *Guidance on Toxicology Study Data for Application of Agricultural Chemical Registration.* 59 NohSan No. 4200.

U.S. Environmental Protection Agency. Toxic Substances Control Act (TSCA); Good Laboratory Practice Standards; Final Rule. 40 CFR Part 792.

U.S. Environmental Protection Agency. Federal Insecticide, Fungicide and Rodenticide Act (FIFRA); Good Laboratory Practice Standards; Final Rule. 40 CFR Part 160.

Organization for Economic Cooperation and Development (1992). The OECD Principles of Good Laboratory Practice, Environment Monograph No. 45.

Japanese Ministry of Agriculture, Forestry and Fisheries (1984). *Good Laboratory Practice Standards.* 59 NohSan No. 3850.

REGULATORY COMPLIANCE

This study will be conducted in compliance with the Good Laboratory Practice (GLP) regulations cited above.

All changes or revisions of this protocol shall be documented, signed by the Study Director and the Sponsor, dated and maintained with the protocol.

The Quality Assurance Unit (QAU) will audit the protocol, the raw data and the report, and will inspect critical phases of the study in accordance with the Standard Operating Procedures of Argus Research Laboratories, Inc.

The final report will include a statement signed by the Study Director that the report accurately reflects the raw data obtained during the performance of the study and that all applicable GLP regulations were followed in the conduct of the study. Should

significant deviations from GLP regulations occur, each will be described in detail, together with how the deviation might affect the quality or integrity of the study.

SCHEMATIC OF STUDY DESIGN AND STUDY SCHEDULE:

See ATTACHMENT 1 to the protocol.

TEST SUBSTANCE AND CARRIER:

Identification:

Test Substance:

Ammonium Perchlorate (source and lot identification will be added prior to finalization or documented in the raw data).

Carrier:

Reverse osmosis membrane processed deionized water (R.O. deionized water). Results of R.O. deionized water analyses will be included in the raw data and the final report.

Neither the Sponsor nor the Study Director is aware of any potential contaminants likely to be present in the carrier that would interfere with the results of this study. Therefore, no analyses other than those mentioned in this protocol will be conducted.

Safety Precautions:

Gloves, mask, appropriate eye protection, full Tyvek® suit and half-face respirator to be worn during formulation preparation. The Material Safety Data Sheet (MSDS) is attached to the protocol (see ATTACHMENT 2).

Storage:

Bulk Test Substance:	Room temperature.
Carrier:	Room temperature.
Prepared Formulations:	Prepared stock formulations will be stored refrigerated. Dosage solutions will be allowed to equilibrate to room temperature prior to use.

All test substance shipments to the Testing Facility should be addressed to the attention of Julian Gulbinski, Manager of Formulations, at the previously cited address and telephone number.

Shipments should include information concerning storage conditions and shipping cartons should be labeled appropriately. The recipient should be notified in advance of sample shipment.

FORMULATION:

Frequency of Preparation:

Formulations of the test substance will be prepared weekly at the Testing Facility. Detailed preparation procedures will be attached to this protocol (ATTACHMENT 3).

Adjustment for Purity:

The test substance will be considered 100% active for the purpose of dosage calculations.

Testing Facility Reserve Samples:

The Testing Facility will reserve a 5 g sample of each lot of bulk test substance and a 5 mL sample of the carrier used during the course of the study. Samples will be stored under the previously cited conditions.

ANALYSES:

Samples additional to those described below may be taken if deemed necessary during the course of the study.

Bulk Test Substance Sampling:

A 1 g sample of the test substance will be taken on the last day of treatment and sent (ambient conditions) to the Supplier for analysis.

The recipient's name, address and telephone number will be added to the protocol prior to finalization or by amendment. The recipient will be notified in advance of sample shipment.

Concentration Analyses:

Concentration of the test substance in prepared solutions will be verified during the course of this study. Duplicate samples (10 mL each) will be taken from each formulation (including stock solution) on the day of the first and last preparation. One sample of each duplicate set will be shipped for analysis; the remaining samples will be retained at the Testing Facility as backup samples. Backup samples will be stored under the previously cited conditions and discarded at the Testing Facility following report finalization.

Stability of Prepared Solutions:

Documentation of the stability of the prepared solutions, at concentrations that bracket the range to be used in this study, is on file with the Sponsor. Stability has been established for up to 109 days.

Shipping Instructions:

Samples to be analyzed will be shipped (refrigerated) to:

Gloria Gates, B.S.
Lancaster Laboratories, Inc.
2425 New Holland Pike
Lancaster, Pennsylvania 17601
Telephone: (717) 656-2301

The recipient will be notified in advance of sample shipment.

DISPOSITION:

All remaining bulk test substance and prepared formulations will be discarded at the Testing Facility.

TEST SYSTEM:

Species/Strain and Reason for Selection:

The New Zealand White [Hra:(NZW)SPF] rabbit was selected as the Test System because: 1) it is one non-rodent mammalian species accepted and widely used throughout the industry for nonclinical studies of developmental toxicity (embryo-fetal toxicity/teratogenicity); 2) this strain of rabbit has been demonstrated to be sensitive to developmental toxins; 3) historical data and experience exist at the Testing Facility[1-3]; and 4) the test substance is pharmacologically active in the species and strain.

Number and Sex:

Population evaluated: 25 timed pregnant female rabbits (5 per dosage group).

Body Weight and Age:

The individual body weights of the female rabbits will range from 2.5 kg to 5.5 kg; the rabbits will be approximately five to seven months of age at the time of study assignment. Actual body weights recorded at receipt and at study assignment will be documented in the raw data.

Source:

Covance Research Products, Inc.
Swampbridge Road, Box 7200
Denver, Pennsylvania 17517

The rabbits will be shipped in filtered cartons by truck from Covance Research Products, Inc., Denver, Pennsylvania, to the Testing Facility.

Identification:

Rabbits are permanently identified using Monel® self-piercing ear tags (Gey Band and Tag Co., Inc., No. MSPT 20103). Female rabbits are assigned temporary numbers at receipt and are given unique permanent identification numbers when assigned to the study on the basis of day 0 of presumed gestation body weights.

ANIMAL HUSBANDRY:

All cage sizes are in compliance with the *Guide for the Care and Use of Laboratory Animals*[4].

Housing:

The rabbits will be individually housed in units of six to eight stainless-steel cages. No nesting materials will be supplied because the female rabbits will be sacrificed before parturition is expected.

Room Air, Temperature and Humidity:

The animal room is independently supplied with at least ten changes per hour of 100% fresh air that has been passed through 99.97% HEPA filters. Room temperature will be maintained at 61°F (16°C) to 72°F (22°C) and monitored constantly. Room humidity will also be monitored constantly and maintained at 30% to 70%.

Light:

An automatically-controlled 12-hour light:12-hour dark fluorescent light cycle will be maintained. Each dark period will begin at 1900 hours EST.

Diet:

Approximately 150 g of Certified Rabbit Chow® #5322 (PMI Nutrition International) will be available to each rabbit each day until the first day of dosage, at which time approximately 180 g of the same certified feed will be offered to each rabbit each day.

The certified feed will be available from individual stainless-steel "J-type" feeders attached to each cage.

Water:

Chlorine will not be added to the R.O. water as a bacteriostat during the acclimation and exposure period.

All water will be from a local source and passed through a reverse osmosis membrane before use. Water is analyzed monthly for possible bacterial contamination and twice annually for possible chemical contamination.

During the acclimation and pre-exposure periods, rabbits will be given R.O. deionized water only available *ad libitum* from individual amber bottles attached to the cages. During the exposure period, rabbits will be given either R.O. deionized water only (carrier control group) or test drinking water prepared using R.O. deionized water and the test substance. These will be available *ad libitum* from individual bottles attached to the cages.

Contaminants:

Neither the Sponsor nor the Study Director is aware of any potential contaminants likely to be present in the certified diet or in the drinking water at levels that would interfere with the results of this study. Therefore, no analyses other than those routinely performed by the feed supplier or those mentioned in this protocol will be conducted.

MATING AND RANDOMIZATION:

The female rabbits will be naturally bred at the Supplier, by breeder male rabbits of the same source and strain, before shipment to the Testing Facility. The day mating occurs will be designated day 0 of presumed gestation. The rabbits will be shipped to the Testing Facility after mating, to arrive on day 2 of presumed gestation. Before shipment of the rabbits, the Supplier will forward breeding records and day 0 of presumed gestation body weights. A computer-generated (weight-ordered) randomization procedure will be used to assign the rabbits to dosage groups based on this information.

ADMINISTRATION:

Route and Reason for Choice:

The oral (drinking water) route was selected for use because it is the most likely route of human exposure.

Method and Frequency:

A constant concentration (%) of the test substance equivalent to the target doses specified in the table below will be offered to the rabbits in the drinking water on days 6 through 28 of presumed gestation. The actual dosages in mg/kg/day consumed will be calculated and presented for periods corresponding to body weight and water consumption observations. Concentrations may be adjusted, if necessary, based on these calculations, to more closely match the target dosage levels.

Rationale for Dosage Selection:

Dosages were selected by the Sponsor on the basis of available data.

Target Dosages and Concentrations:

Group	Target Dosage (mg/kg/day)	Concentration (µg/mL)[a]	Number of Female Rabbits
1	0 (Carrier)	0	5
2	0.1	1.0	5
3	1.0	10.0	5
4	10.0	100.0	5
5	20.0	200.0	5

The test article will be considered 100% active for the purpose of dosage calculations.

a. Based on average water consumption of 400 mL/animal/day (100 mL/kg/day) for a 4 Kg female rabbit. These concentrations will be adjusted weekly based on actual body weight and water consumption levels recorded the previous week.

TESTS, ANALYSES AND MEASUREMENTS:

Viability:

All Periods: At least twice daily.

Clinical Observations and/or General Appearance:

Predosage Period: At least once.

Dosage Period: Daily and on day of sacrifice.

Clinical observations may be recorded more frequently than cited above, if deemed appropriate by the Study Director and/or Study Monitor.

Body Weights:

Predosage Period:	Days 0 and 5 of presumed gestation and on the day of arrival (Day 2 of presumed gestation) at the Testing Facility (values will not be tabulated).
Dosage Period:	Daily.
Day of Sacrifice:	Terminal weight.

Feed Consumption Values:

Predosage Period:	Recorded daily after arrival at the Testing Facility (values not tabulated).
Dosage Period:	Recorded daily. Rabbits will be monitored daily for hydration.
Day of Sacrifice	Feed left recorded.

Feed consumption values during the dosing period will be tabulated for the same intervals as body weight evaluations.

Water Consumption Values (recorded and tabulated):

Predosage Period:	Daily.
Dosage Period:	Daily.
Day of Sacrifice:	Water left recorded.

Caesarean-Sectioning Observations:

Rabbits will be Caesarean-sectioned on day 29 of presumed gestation. The gravid uterus will be excised and weighed. The fetuses will be removed from the uterus and placed in individual containers. The rabbits will be examined for number and distribution of:

Corpora Lutea.

Implantation Sites.

Live and Dead Fetuses.
(A live fetus is defined as one that responds to stimuli; a dead fetus is defined as a term fetus that does not respond to stimuli and that is not markedly autolyzed; dead fetuses demonstrating marked to extreme autolysis are considered to be late resorptions.)

Early and Late Resorptions.
(A conceptus is defined as a late resorption if it is grossly evident that organogenesis has occurred; if this is not the case, the conceptus is identified as an early resorption.)

Fetal Observations:

Body Weights:

The body weight of each fetus will be recorded. Only body weights of live fetuses will be used to determine litter fetal body weight averages.

Gross External Alterations:

All fetuses will be examined for gross external alterations. Late resorptions and dead fetuses also will be examined for gross external alterations to the extent possible but such observations will not be included in either data summarization or statistical analyses. Fetuses with gross external alterations will be preserved in neutral buffered 10% formalin. All other fetuses will be discarded.

Representative photographs of fetal gross alterations will be taken.

Sex:

All fetuses will be examined internally to determine sex.

METHOD OF SACRIFICE, BLOOD COLLECTION AND NECROPSY:

Rabbits will be anethesized on day 29 of presumed gestation with an intravenous sodium pentobarbital solution followed by blood collection from the inferior vena cava and exsanguination. Live fetuses will be sacrificed by an intraperitoneal injection of an appropriate euthanasia solution (Beuthanasia®-D Special, manufactured by Schering-Plough Animal Health). Rabbits will not be fasted prior to sample collection and euthanasia. The blood samples will be obtained prior to necropsy and the time of sample collection will be recorded for each rabbit. Throughout the euthanasia and necropsy procedures, every effort will be made to avoid inducing stress in the rabbits since this could affect scheduled hormone evaluations (e.g., no excess noise or radio).

Blood Collection:

Approximately 3 mL of blood will be collected in a serum separator tube to yield approximately 1500 µL of serum. The serum will be aliquoted into three vials (approximately 500 µL/vial) for TSH, T_3 and T_4 samples, and frozen on dry ice. Serum will be maintained frozen at -70°C until the conclusion of the study.

Serum samples will be shipped, frozen on dry ice (laboratory and address to be added by amendment). The recipient will be notified in advance of sample shipment.

Gross Necropsy and Histology:

Scheduled Sacrifice:

On day 29 of presumed gestation, female rabbits will be Caesarean-sectioned, and a gross necropsy of the thoracic, abdominal and pelvic viscera will be performed. Uteri of apparently nonpregnant does will be stained with 10% ammonium sulfide to confirm the absence of implantation sites[5].

Rabbits Found Dead or Moribund:

Any rabbits showing signs of severe debility or toxicity, particularly if death appears imminent, will be sacrificed for humane reasons and to prevent loss of tissues through autolysis.

Rabbits that die or are sacrificed because of moribund condition, abortion or premature delivery will be examined for the cause of death or moribund condition on the day the observation is made. Pregnancy status and uterine contents will be recorded. Aborted fetuses and/or delivered pups will be examined to the extent possible, using the same methods described for fetuses. Uteri of apparently nonpregnant does will be stained with 10% ammonium sulfide to confirm the absence of implantation sites[5].

Gross Necropsy

Gross lesions will be retained in neutral buffered 10% formalin for possible future evaluation. (Exception: Parovarian cysts will be discarded; these are common, spontaneous lesions in rabbits.) Unless specifically cited below, all other tissues will be discarded.

Gravid uterine weights will be recorded at scheduled sacrifice on day 29 of presumed gestation. Gravid uterine weights will not be recorded for rabbits that do not survive until the scheduled day of termination.

Thyroid/Parathyroid Collection:

The thyroids glands, parathyroids glands and section of the trachea of all rabbits will be immersed in fixative immediately after collection. Following fixation, the thyroid/parathyroid tissue samples will be carefully trimmed and weighed. The same technician will perform all trimming of the thyroid/parathyroid tissues beginning at least 48 hours post fixation. Organ weights will be recorded.

Shipment of Tissue Samples:

Tissue samples will be shipped to the address cited below for histological analysis:

W. Ray Brown, D.V.M., Ph.D.
Veterinary Pathologist
Research Pathology Services, Inc.
438 E. Butler Avenue
New Britain, Pennsylvania 18901
Telephone: (215) 345-7070
Telefax: (215) 345-4326

The recipient will be notified in advance of sample shipment.

STATISTICAL EVALUATION:

Averages and percentages will be calculated. Litter values will be used where appropriate. Additional procedures and/or analyses may be performed if deemed appropriate.

DATA ACQUISITION, VERIFICATION AND STORAGE:

Data will be hand- and/or computer-recorded. Records will be reviewed by the Study Director and/or appropriate management personnel within 21 days after generation. All original records will be stored in the archives of the Testing Facility. All original data will be bound and indexed. A copy of all raw data will be supplied to the Sponsor upon request. Preserved tissues will be stored at the Testing Facility at no charge for one year after mailing of the draft final report, after which time the Sponsor will be contacted to determine the disposition of these materials.

RECORDS TO BE MAINTAINED:

Protocol and Amendments.
Test Substance, Vehicle and/or Reagent Receipt, Preparation and Use.
Animal Acquisition.
Randomization Schedules.
Veterinarian Examination.

Mating History.
Treatment (if prescribed by Staff Veterinarian).
General Comments.
Clinical Observations and/or General Appearance.
Blood Sample Collection, Processing and Shipment (if required).
Body Weights.
Feed Consumption Values.
Water Consumption Values.
Caesarean-Sectioning and Fetal Observations.
Gross Necropsy Observations.
Organ Weights.
Photographs (if required).
Study Maintenance (room and environmental records).
Feed and Water Analyses.
Packing and/or Shipment Lists.

KEY PERSONNEL:

Executive Director of Research: Mildred S. Christian, Ph.D., ATS
Director of Research: Alan M. Hoberman, Ph.D., DABT
Associate Director of Research and Study Director: Raymond G. York, Ph.D., DABT
Director of Laboratory Operations: John F. Barnett, B.S.
Manager of Study Coordination: Valerie A. Sharper, M.S.
Manager of Animal Operations and Chairperson, Institutional Animal Care and Use Committee: Dena C. Lebo, V.M.D.
Manager of Regulatory Compliance: Kathleen A. Moran, M.S.
Consultant, Veterinary Pathology: W. Ray Brown, D.V.M., Ph.D., ACVP

REPORT:

An unaudited letter report for the purpose of dosage selection for the full study will be prepared immediately following completion of the in-life phase.

An audited report will be prepared including: abstract, summaries of the methods, results and conclusion; table of contents; Study Director's GLP compliance statement; copy of the protocol; amendments and deviations; QAU statement; summary and individual tables; and reports of supporting data (if appropriate). The report will not be included as an appendix to the full study report. The Sponsor will receive one copy of the draft report and two copies of the final report.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE STATEMENT:

The procedures described in this protocol have been reviewed by the Testing Facility's Institutional Animal Care and Use Committee. All procedures described in this protocol that involve study animals will be conducted in a manner to avoid or minimize discomfort, distress or pain to the animals.

The Sponsor's signature below documents the fact that this is not an unnecessarily duplicative study, and that no alternative (*in vitro*) procedures were available for meeting the stated purposes of the study.

REFERENCES:

1. Christian, M.S., Hoberman, A.M. and Smith, T.H.F. (1982). Dosage-range study of the teratogenic potential of suspensions of trinitrofluorenone (TNF) administered orally to New Zealand White rabbits. Toxicologist 2(1):40 (#143).

2. Christian, M.S. (1984). Reproductive toxicity and teratology evaluations of naltrexone (Proceedings of Naltrexone Symposium, New York Academy of Sciences, November 7, 1983), J. Clin. Psychiat. 45(9):7-10.

3. Feussner, E.L., Lightkep, G.E., Hennesy, R.A., Hoberman, A.M. and Christian, M.S. (1992). A decade of rabbit fertility data: Study of historical control animals. Teratology 46(4):349-365.

4. Institute of Laboratory Animal Resources (1996). *Guide for the Care and Use of Laboratory Animals*. National Academy Press, Washington, D.C.

5. Salewski, E. (1964). Färbemethode zum makroskopischen Nachweis von Implantationsstellen am Uterus der Ratte. Arch. Pathol. Exp. Pharmakol. 247:367.

PROTOCOL APPROVAL:

FOR THE TESTING FACILITY

Alan M. Hoberman, Ph.D., DABT
Director of Research

18-Dec-97
Date

Raymond G. York, Ph.D., DABT
Associate Director of Research and
Study Director

18-DEC-97
Date

Dena C. Lebo, V.M.D.
Chairperson, Institutional Animal Care and
Use Committee

18 Dec 97
Date

FOR THE SPONSOR

Michael F. Girard
Perchlorate Study Group Representative
Study Monitor

19 DEC 1997
Date

Michael L. Dourson, Ph.D., DABT
Toxicology Excellence for Risk Assessment (TERA)
Scientific Advisor

12-26-97
Date

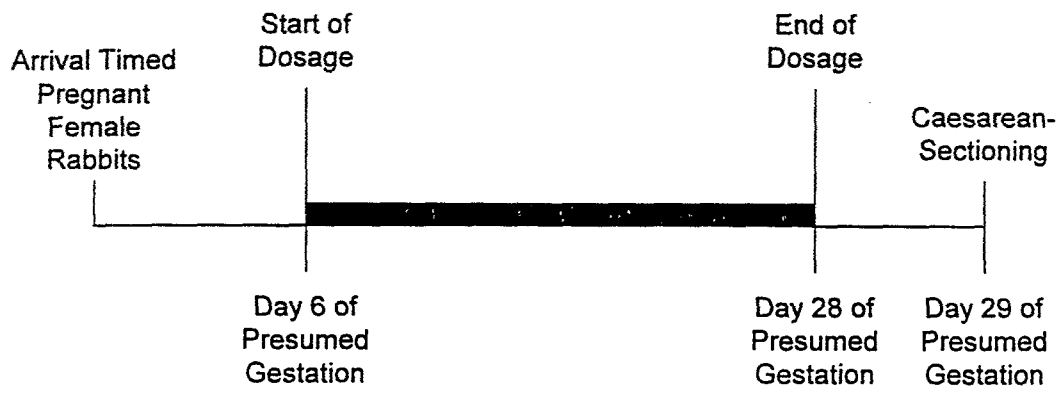
ATTACHMENT 1

SCHEMATIC OF STUDY DESIGN AND STUDY SCHEDULE

ATTACHMENT 1

Study Schematic

Dosage-Range Developmental Toxicity Study [a]



= Dosage Period

a = For additional details see "Tests, Analyses and Measurements" section of the protocol.

SCHEDULE[a]

19 DEC 97	Animals Arrive - Acclimation Begins.
23 DEC 97 - 14 JAN 98	Dosage Period (Days 6 through 28 of presumed gestation).
15 JAN 98	Caesarean-Sectioning Period (Day 29 of presumed gestation).
23 JAN 98	Unaudited Letter Report.
26 MAR 98	Audited Summary Report.

---

a. The study initiation date is the date the Study Director signs the protocol.

ATTACHMENT 2

MATERIAL SAFETY DATA SHEET

PRODUCT #: 208507 NAME: AMMONIUM PERCHLORATE, 99.8%
MATERIAL SAFETY DATA SHEET, Valid 5/97 - 7/97
Printed Monday, July 14, 1997 9:22AM

Sigma Chemical Co.
P.O. Box 14508
St. Louis, MO 63178
Phone: 314-771-5765

Aldrich Chemical Co., Inc.
1001 West St. Paul
Milwaukee, WI 53233
Phone: 414-273-3850

Fluka Chemical Corp.
1001 West St. Paul
Milwaukee, WI 53233
Phone: 414-273-3850

SECTION 1. - - - - - - - - - - CHEMICAL IDENTIFICATION- - - - - - - - - -
CATALOG #: 208507
NAME: AMMONIUM PERCHLORATE, 99.8%
SECTION 2. - - - - - - COMPOSITION/INFORMATION ON INGREDIENTS - - - - - -
CAS #: 7790-98-9
MF: H4CLNO4
EC NO: 232-235-1
SYNONYMS
AMMONIUM PERCHLORATE (DOT) * UN0402 (DOT) * UN1442 (DOT) *
SECTION 3. - - - - - - - - - - HAZARDS IDENTIFICATION - - - - - - - - - -
LABEL PRECAUTIONARY STATEMENTS
EXPLOSIVE
HARMFUL
HEATING MAY CAUSE AN EXPLOSION.
CONTACT WITH COMBUSTIBLE MATERIAL MAY CAUSE FIRE.
HARMFUL IF SWALLOWED.
IRRITATING TO EYES, RESPIRATORY SYSTEM AND SKIN.
STRONG OXIDIZER.
KEEP AWAY FROM HEAT
IN CASE OF CONTACT WITH EYES, RINSE IMMEDIATELY WITH PLENTY OF WATER AND SEEK MEDICAL ADVICE.
TAKE OFF IMMEDIATELY ALL CONTAMINATED CLOTHING.
WEAR SUITABLE PROTECTIVE CLOTHING, GLOVES AND EYE/FACE PROTECTION.
SECTION 4. - - - - - - - - - - FIRST-AID MEASURES- - - - - - - - - - -
IN CASE OF CONTACT, IMMEDIATELY FLUSH EYES OR SKIN WITH COPIOUS AMOUNTS OF WATER FOR AT LEAST 15 MINUTES WHILE REMOVING CONTAMINATED CLOTHING AND SHOES.
IF INHALED, REMOVE TO FRESH AIR. IF NOT BREATHING GIVE ARTIFICIAL RESPIRATION. IF BREATHING IS DIFFICULT, GIVE OXYGEN.
IF SWALLOWED, WASH OUT MOUTH WITH WATER PROVIDED PERSON IS CONSCIOUS.
CALL A PHYSICIAN.
DISCARD CONTAMINATED CLOTHING AND SHOES.
SECTION 5. - - - - - - - - - - FIRE FIGHTING MEASURES - - - - - - - - - -
EXTINGUISHING MEDIA
WATER SPRAY.
SPECIAL FIREFIGHTING PROCEDURES
WEAR SELF-CONTAINED BREATHING APPARATUS AND PROTECTIVE CLOTHING TO PREVENT CONTACT WITH SKIN AND EYES.
USE WATER SPRAY TO COOL FIRE-EXPOSED CONTAINERS.
STRONG OXIDIZER.
UNUSUAL FIRE AND EXPLOSIONS HAZARDS
MAY EXPLODE WHEN HEATED.
CONTACT WITH OTHER MATERIAL MAY CAUSE FIRE.
EMITS TOXIC FUMES UNDER FIRE CONDITIONS.
SECTION 6. - - - - - - - - - ACCIDENTAL RELEASE MEASURES- - - - - - - - -

EVACUATE AREA.
WEAR SELF-CONTAINED BREATHING APPARATUS, RUBBER BOOTS AND HEAVY RUBBER GLOVES.
COVER WITH DRY LIME OR SODA ASH, PICK UP, KEEP IN A CLOSED CONTAINER AND HOLD FOR WASTE DISPOSAL.
VENTILATE AREA AND WASH SPILL SITE AFTER MATERIAL PICKUP IS COMPLETE.

SECTION 7. - - - - - - - - - - HANDLING AND STORAGE- - - - - - - - - - -

REFER TO SECTION 8.

ADDITIONAL INFORMATION

MIXTURES OF AMMONIUM PERCHLORATE WITH SULFUR, ORGANIC MATERIALS, FINELY DIVIDED METALS ARE EXPLOSIVE AND HAVE A SHOCK-SENSITIVITY EQUIVALENT TO PICRIC ACID. IT IS INCOMPATIBLE WITH ALUMINUM, COPPER, CARBON, POTASSIUM PERMANGANATE, POTASSIUM PERIODATE, POTASSIUM DICHROMATE, CADMIUM OXIDE, COPPER OXIDE, ZINC OXIDE, IRON OXIDE, DICHROMIUM TRIOXIDE, COPPER CHROMITE, METAL PERCHLORATES ALL OF WHICH CONSIDERABLY LOWER ITS EXPLOSION TEMPERATURE OF 440 C AND INCREASE ITS SENSITIVITY TO FRICTION. MIXTURES WITH PHOSPHOROUS ARE SHOCK-SENSITIVE. REACTS VIOLENTLY WITH CHLORINE OR CHLORINE DIOXIDE, EXPLOSIONS MAY RESULT.

SECTION 8. - - - - - - EXPOSURE CONTROLS/PERSONAL PROTECTION- - - - - -

WEAR APPROPRIATE NIOSH/MSHA-APPROVED RESPIRATOR, CHEMICAL-RESISTANT GLOVES, SAFETY GOGGLES, OTHER PROTECTIVE CLOTHING.
SAFETY SHOWER AND EYE BATH.
USE ONLY IN A CHEMICAL FUME HOOD.
DO NOT BREATHE DUST.
DO NOT GET IN EYES, ON SKIN, ON CLOTHING.
AVOID PROLONGED OR REPEATED EXPOSURE.
WASH THOROUGHLY AFTER HANDLING.
HARMFUL SOLID.
IRRITANT.
KEEP TIGHTLY CLOSED.
KEEP AWAY FROM COMBUSTIBLE MATERIALS, HEAT, SPARKS, AND OPEN FLAME.
STORE IN A COOL DRY PLACE.

SECTION 9. - - - - - - - - PHYSICAL AND CHEMICAL PROPERTIES - - - - - - - -

APPEARANCE AND ODOR

WHITE POWDER

PHYSICAL PROPERTIES

SPECIFIC GRAVITY: 1.950

SECTION 10. - - - - - - - - -STABILITY AND REACTIVITY - - - - - - - - -

INCOMPATIBILITIES

STRONG REDUCING AGENTS
STRONG ACIDS
HEAT-SENSITIVE.

HAZARDOUS COMBUSTION OR DECOMPOSITION PRODUCTS

AMMONIA

SECTION 11. - - - - - - - - - - TOXICOLOGICAL INFORMATION - - - - - - - -

ACUTE EFFECTS

HARMFUL IF SWALLOWED.
MAY BE HARMFUL IF INHALED.
MAY BE HARMFUL IF ABSORBED THROUGH THE SKIN.
CAUSES EYE AND SKIN IRRITATION.
MATERIAL IS IRRITATING TO MUCOUS MEMBRANES AND UPPER RESPIRATORY TRACT.

RTECS #: SC7520000

PERCHLORIC ACID, AMMONIUM SALT
TOXICITY DATA

ORL-RAT LD50:4200 MG/KG	GISAAA 28(8),8,63
ORL-MUS LD50:1900 MG/KG	GISAAA 28(8),8,63
ORL-RBT LD50:1900 MG/KG	GISAAA 28(8),8,63
ORL-GPG LD50:3310 MG/KG	GISAAA 28(8),8,63

TARGET ORGAN DATA
BEHAVIORAL (CONVULSIONS OR EFFECT ON SEIZURE THRESHOLD)
BEHAVIORAL (EXCITEMENT)
BEHAVIORAL (ATAXIA)
BEHAVIORAL (COMA)
LUNGS, THORAX OR RESPIRATION (DYSPNAE)
ONLY SELECTED REGISTRY OF TOXIC EFFECTS OF CHEMICAL SUBSTANCES (RTECS) DATA IS PRESENTED HERE. SEE ACTUAL ENTRY IN RTECS FOR COMPLETE INFORMATION.

SECTION 12. - - - - - - - - - - ECOLOGICAL INFORMATION - - - - - - - - - -
DATA NOT YET AVAILABLE.

SECTION 13. - - - - - - - - - - DISPOSAL CONSIDERATIONS - - - - - - - - -
FOR SMALL QUANTITIES: CAUTIOUSLY ADD TO A LARGE STIRRED EXCESS OF WATER. ADJUST THE PH TO NEUTRAL, SEPARATE ANY INSOLUBLE SOLIDS OR LIQUIDS AND PACKAGE THEM FOR HAZARDOUS-WASTE DISPOSAL. FLUSH THE AQUEOUS SOLUTION DOWN THE DRAIN WITH PLENTY OF WATER. THE HYDROLYSIS AND NEUTRALIZATION REACTIONS MAY GENERATE HEAT AND FUMES WHICH CAN BE CONTROLLED BY THE RATE OF ADDITION.
OBSERVE ALL FEDERAL, STATE AND LOCAL ENVIRONMENTAL REGULATIONS.

SECTION 14. - - - - - - - - - - TRANSPORT INFORMATION - - - - - - - - -
CONTACT ALDRICH CHEMICAL COMPANY FOR TRANSPORTATION INFORMATION.

SECTION 15. - - - - - - - - - - REGULATORY INFORMATION - - - - - - - - - -
EUROPEAN INFORMATION
EC INDEX NO: 017-009-00-0
EXPLOSIVE
HARMFUL
R 9
EXPLOSIVE WHEN MIXED WITH COMBUSTIBLE MATERIAL.
R 44
RISK OF EXPLOSION IF HEATED UNDER CONFINEMENT.
S 25
AVOID CONTACT WITH EYES.
S 16
KEEP AWAY FROM SOURCES OF IGNITION - NO SMOKING.
S 27
TAKE OFF IMMEDIATELY ALL CONTAMINATED CLOTHING.
S 24/25
AVOID CONTACT WITH SKIN AND EYES.
REVIEWS, STANDARDS, AND REGULATIONS
OEL=MAK
NOHS 1974: HZD 80353; NIS 2; TNF 101; NOS 3; TNE 1062
NOES 1983: HZD 80353; NIS 1; TNF 7; NOS 1; TNE 1445; TFE 230
EPA TSCA SECTION 8(B) CHEMICAL INVENTORY

SECTION 16. - - - - - - - - - - OTHER INFORMATION- - - - - - - - - - -
THE ABOVE INFORMATION IS BELIEVED TO BE CORRECT BUT DOES NOT PURPORT TO BE ALL INCLUSIVE AND SHALL BE USED ONLY AS A GUIDE. SIGMA, ALDRICH, FLUKA SHALL NOT BE HELD LIABLE FOR ANY DAMAGE RESULTING FROM HANDLING OR FROM CONTACT WITH THE ABOVE PRODUCT. SEE REVERSE SIDE OF INVOICE OR

PACKING SLIP FOR ADDITIONAL TERMS AND CONDITIONS OF SALE.
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FLUKA CHEMIE AG
LICENSE GRANTED TO MAKE UNLIMITED PAPER COPIES FOR INTERNAL USE ONLY

ATTACHMENT 3

TEST SUBSTANCE PREPARATION PROCEDURE

ATTACHMENT 3

TEST SUBSTANCE PREPARATION PROCEDURE

Test Substance: Ammonium Perchlorate
Vehicle: R.O. deionized water

A. Purpose:

The purpose of this procedure is to provide a method for the preparation of dosage solutions of ammonium perchlorate for oral administration to rabbits on Argus Study 1416-002P.

B. General Information:

1. All solution containers will be labeled and color-coded. Each label will specify the protocol number, test substance identification, Argus batch number, concentration, dosage level, preparation date, expiration date and storage conditions.

2. Solutions will be prepared:

__ Daily _X_ Weekly __ For _ days of use
__ As required by Protocol __ By Sponsor

3. Solutions will be prepared from 1 stock solution (50 mg/mL, w:v) and diluted to each respective concentration. Stock solution will be prepared at least once. NOTE: Stock solution will be stored refrigerated and may appear cloudy.

4. Safety:

_X_ Gloves, lab coat, goggles or safety glasses and faceshield
__ Dust-Mist Respirator
_X_ Half-Face Respirator or/Positive Pressure Hood
__ Full-Face Respirator/Positive Pressure Hood
_X_ Tyvek Apron and Sleeves or Tyvek suit
_X_ Prepared in a Fume Hood
_X_ Explosive (avoid contact with metals or reducing agents)

5. Dosage solutions adjusted for % Purity or Correction Factor:

__ Yes _X_ No (Calculations based on 100%)
__ % Activity ___% Purity __ Correction Factor

6. Sampling requirements: Cited in protocol.

TEST SUBSTANCE PREPARATION PROCEDURE

7. Storage: Cited in protocol.

NOTE: Prior to test substance preparation, accurately precalibrate the preparation vessels. Measure the required amount of the vehicle into a graduated cylinder, and pour the required amount of vehicle into the vessel. Carefully mark the meniscus on each vessel.

C. Stock Solution Preparation

1. Prepare a stock solution of test substance by accurately weighing the required amount of test substance to an appropriately labeled container. (see PREPARATION CALCULATIONS).

2. Add approximately 80% of vehicle to the container (see PREPARATION CALCULATIONS).

3. Q.S. to final volume with vehicle (see PREPARATION CALCULATIONS).

4. Add a stirbar to the container, place on a magnetic stirplate and agitate until test article has mixed.

D. Dosage Solution Preparation:

1. Measure the required amount of test substance stock solution that is needed for the appropriate dosage level into an appropriately sized, labeled container (see PREPARATION DILUTION CALCULATIONS).

2. Add approximately 80% of vehicle to the container (see PREPARATION DILUTION CALCULATIONS).

3. Q.S. to final volume with vehicle (see PREPARATION DILUTIONS CALCULATIONS).

4. Add a stirbar to the container, place on a magnetic stirplate and agitate until test article has mixed.

5. Cover and mix by inversion.

6. Repeat steps (1) through (5) for each concentration.

ATTACHMENT 3

TEST SUBSTANCE PREPARATION PROCEDURE

Written By: Julian Gilbreath

Approved by: Raymond A. Hyson Date: 17-DEC-97

Clarification: X No ___ Yes [see attached clarification form]

Initials/Date: JG 1-22-98

RESEARCH Argus LABORATORIES

Argus Research Laboratories, Inc.
905 Sheehy Drive, Building A
Horsham, Pennsylvania 19044
T: (215) 443-8710 F: (215) 443-8587

PROTOCOL 1416-002P

ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

Amendment 1 - December 30, 1997

---

1. Target Dosages and Concentration (page 8 of the protocol):

   Target dosages for Groups 2 and 3 will be changed to 50 and 100 mg/kg/day at concentrations of 500.0 and 1000.0 μg/mL, respectively, from the original 0.1 and 1.0 mg/kg/day dosages at concentrations of 1.0 and 10.0 μg/mL, respectively.

   Reason for Change:

   This change was made at the request of the Sponsor to elicit maternal toxicity.

30-Dec-97
Alan M. Hoberman, Ph.D., DABT Date
Director of Research

30-DEC-97
Raymond G. York, Ph.D., DABT Date
Associate Director of Research and
Study Director

30 Dec 97
Dena C. Lebo, V.M.D. Date
Chairperson, Institutional Animal Care
and Use Committee

5 JAN 98
Michael F. Girard Date
Perchlorate Study Group Representative
Study Monitor

1.3.98
Michael L. Dourson, Ph.D., DABT Date
Toxicology Excellence for Risk Assessment (TERA)
Scientific Advisor

RESEARCH Argus LABORATORIES

Argus Research Laboratories, Inc.
905 Sheehy Drive, Building A
Horsham, Pennsylvania 19044
T: (215) 443-8710 F: (215) 443-8587

PROTOCOL 1416-002P

ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

Amendment 2 - January 16, 1998

---

1. Blood Collection (page 11 of the protocol):

   Serum samples for TSH, T_3 and T_4 analyses will be shipped frozen on dry ice to the attention of:

   Dr. Saroj R. Das
   President
   AniLytics, Inc.
   200 Girard Street, Suite 200
   Gaithersburg, Maryland 20877
   Telephone: (301) 921-0168
   Telefax: (301) 977-0433

Reason for Change:

This information was to be added by amendment to the protocol.

16 JAN 98
Alan M. Hoberman, Ph.D., DABT Date
Director of Research

16-JAN-98
Raymond G. York, Ph.D., DABT Date
Associate Director of Research and
Study Director

16 Jan 98
Dena C. Lebo, V.M.D. Date
Chairperson, Institutional Animal Care
and Use Committee

1/23/98
Michael F. Girard Date
Perchlorate Study Group Representative
Study Monitor

4-6-98
Michael L. Dourson, Ph.D., DABT Date
Toxicology Excellence for Risk Assessment (TERA)
Scientific Advisor

RESEARCH Argus LABORATORIES

Argus Research Laboratories, Inc.
905 Sheehy Drive, Building A
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T: (215) 443-8710 F: (215) 443-8587

PROTOCOL 1416-002P

ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS

Amendment 3 - March 11, 1998

---

1. Disposition (page 5 of the protocol):

   Remaining bulk test substance will be used in additional studies being conducted by the Sponsor, rather than discarded.

   Reason for Change:

   This change clarifies the protocol.

11-MAR-98
Alan M. Hoberman, Ph.D., DABT Date
Director of Research

11-MAR-98
Raymond G. York, Ph.D., DABT Date
Associate Director of Research and
Study Director

11 Mar 98
Dena C. Lebo, V.M.D. Date
Chairperson, Institutional Animal Care
and Use Committee

16 MAR 98
Michael F. Girard Date
Perchlorate Study Group Representative
Study Monitor

3.27.98
Michael L. Dourson, Ph.D., DABT Date
Toxicology Excellence for Risk Assessment (TERA)
Scientific Advisor

ATTACHMENT 2

THYROID HORMONE LEVELS

ANALYTICS INCORPORATED
200 Girard Street, Suite 200, Gaithersburg, MD 20877
301-921-0168 800-237-2815

Client: ARGUS RESEARCH LABORATORIES, INC.
905 SHEEHY DRIVE
BUILDING A
HORSHAM, PA 19044-
(215) 443-8710

Date Collected: 01/15/98
Date Received: 01/20/98
Date Reported: 03/19/98

Client No. 1028 Study: 1416-002P Species: RABBIT

Accession No.	Spec. ID	Gp	Sex	Age	T3,TOTAL NG/DL	T4,TOTAL UG/DL	TSH,LA NG/ML
A 0011316	6726	1	F	7M	133.79	0.64	0.20
A 0011317	6727	1	F	7M	128.68	1.70	0.82
A 0011318	6728	1	F	7M	78.72	1.60	1.03
A 0011319	6729	1	F	7M	143.60	2.52	0.67
A 0011320	6730	1	F	7M	222.37	2.75	1.38
	Mean				141.432	1.842	.82
	S.D.				51.743	.838	.437
Group 1							
A 0011321	6731	2	F	7M	118.94	0.93	0.70
A 0011322	6732	2	F	7M	181.25	2.01	1.48
A 0011323	6733	2	F	7M	99.48	0.64	0.43
A 0011324	6734	2	F	7M	141.60	1.43	0.98
A 0011325	6735	2	F	7M	98.26	0.01	0.19
	Mean				127.906	1.004	.756
	S.D.				34.643	.761	.501
Group 2							
A 0011326	6736	3	F	7M	95.50	0.99	0.50
A 0011327	6737	3	F	7M	37.18	0.00	0.90
A 0011328	6738	3	F	7M	47.82	0.02	0.36
A 0011329	6739	3	F	7M	85.63	1.07	0.49
Reference Range					130 - 143	1.7 - 2.4	0 - 0

ATTACHMENT 3

HISTOPATHOLOGY REPORT

RESEARCH PATHOLOGY SERVICES, INC.

438 East Butler Avenue, New Britain, PA 18901
Phone: 215-345-7070 • Fax: 215-345-4326

ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS PROTOCOL 1416-002P HISTOPATHOLOGY REPORT

SUBMITTED TO:

Raymond G. York, Ph.D., D.A.B.T.
Argus Research Laboratories, Inc.
905 Sheehy Drive
Horsham, PA 19044

SUBMITTED BY:

W Ray Brown Dec. 8, 1998

W. Ray Brown, D.V.M., Ph.D.
Veterinary Pathologist

December 8, 1998

ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS PROTOCOL 1416-002P HISTOPATHOLOGY REPORT

TABLE OF CONTENTS

ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS PROTOCOL 1416-002P HISTOPATHOLOGY REPORT

METHOD:

Microscopic examination was made of the thyroid gland from 25 female New Zealand White [Hra:(NZW)SPF] rabbits equally divided into five treatment groups used in a oral (drinking water) dosage-range developmental toxicity study of ammonium perchlorate. A brief outline of the study design is shown below.

Group	Target Dosage (mg/kg/day)	Concentration (µg/mL)^	Number of Female Rabbits
1	0 (Carrier)	0	5
2	50~	500.0	5
3	100~	1000.0	5
4	10.0	100.0	5
5	20.0	200.0	5

^Based on average water consumption of 400 mL/animal/day (100 mL/kg/day) for a 4kg female rabbit. Concentrations were adjusted weekly based on actual body weight and water consumption levels recorded the previous week. The test substance was considered 100% active for the purpose of dosage calculations.

~Dosages for Groups 2 and 3 were changed from 0.1 and 1.0 mg/kg/day to 50 and 100 mg/kg/day, respectively, on Day 13 of gestation at the request of the sponsor to elicit maternal toxicity.

A constant concentration (%) of the test substance equivalent to the target doses was offered to the female rabbits in the drinking water on Days 6 through 28 of presumed gestation. The actual dosages in mg/kg/day consumed were calculated and presented for periods corresponding to body weight and water consumption observations. The rabbits were euthanized on Day 29 and necropsied.

The in-life portion of the study, necropsies, and recording of the gross necropsy observations were performed by the staff of Argus Research Laboratories, Inc. At necropsy, the thyroid from all female rabbits was excised and retained in 10% neutral buffered formalin and then submitted to Research Pathology Services, Inc. for tissue processing, microscopic slide preparation and histopathologic evaluation. The thyroid glands were routinely processed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for microscopic evaluation.

ORAL (DRINKING WATER) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF AMMONIUM PERCHLORATE IN RABBITS
PROTOCOL 1416-002P
HISTOPATHOLOGY REPORT

Upon completion of the project, all raw data (remaining wet tissue, paraffin blocks, microscopic slides and histology records) will be returned to Argus Research Laboratories, Inc. for archiving.

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RESULTS:

The type, incidence and degree of severity of histomorphologic observations in the thyroid gland of the female rabbits of all groups are summarized in Table 1. The individual histomorphologic findings are presented in Table 2.

Treatment-related microscopic changes were observed in the thyroid gland of rabbits given 20.0, 50, or 100 mg/kg/day of the test substance in the drinking water during gestation. The changes varied somewhat among the groups, but the most common finding was an increased size (hypertrophy) of the thyroid follicular epithelium. The follicles with the follicular-cell hypertrophy were decreased in size and contained a pale, vacuolated colloid. Another finding which was somewhat unusual was very large, cystic and irregularly shaped colloid-filled follicles in two rabbits of the 50 mg/kg/day dosage group. This finding was not observed in any of the other affected rabbits (Table 1).

There were no treatment-related microscopic changes in the thyroid gland of any of the rabbits given 10.0 mg/kg/day of ammonium perchlorate.

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SUMMARY:

Microscopic examination was made of the thyroid gland of four groups of female rabbits (5 rabbits per group) that had been given 10.0, 20.0, 50 or 100 mg/kg/day of ammonium perchlorate in the drinking water in a dosage-range developmental toxicity study. An additional group of 5 female rabbits was given the carrier (reverse-osmosis membrane processed deionized water) and served as controls.

There were no treatment-related microscopic changes in the thyroid gland of any of the rabbits given 10.0 mg/kg/day of ammonium perchlorate during gestation.

Treatment-related microscopic changes were observed in the thyroid gland of rabbits of the 20.0, 50 and 100 mg/kg/day dosage groups. The treatment-related effect consisted primarily of hypertrophy of the follicular epithelial cells. These follicles with the enlarged cells were decreased in size and contained a decreased amount of pale, vacuolated colloid. Another finding seen only in the 50 mg/kg/day dosage group was enlarged, cystic and irregularly shaped follicles in two of the five rabbits.

The treatment-related changes occurred in a varied distribution among the groups without any clear dose response. The most extensive change occurred in rabbits of the 50 mg/kg/day dosage group.

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QUALITY ASSURANCE UNIT STATMENT

All aspects of the tissue processing, microscopic slide preparation, histopathologic evaluation and report preparation for the study listed above have been performed according to the Standard Operating Procedures of Research Pathology Services, Inc. and were audited in accordance with the procedures established by the Quality Assurance Unit of Research Pathology Services, Inc. in compliance with the "Good Laboratory Practice Standards" regulations (21 CFR 58).

Quality Assurance inspections were performed on 01/20/98, 01/23/98, 02/13/98, 02/14/98, 02/17/98, 02/18/98, 02/19/98, 02/20/98, and 12/08/98, and findings were reported to management monthly. There were no deviations from the protocol, Standard Operating Procedures and/or appropriate Good Laboratory Practice regulations noted during the conduct of the study. The summary report of QA inspections was submitted to the Study Director on December 8, 1998.

Karen W. Harkins BS

Karen W. Harkins, BS
Quality Assurance Unit

12-08-98

Date

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Table 1
Incidence and Degree of Severity of Histomorphologic Observations in the Thyroid Gland

Dose Group:	1	2	3	4	5
Sex:	F	F	F	F	F
Number of Animals/Group:	5	5	5	5	5
THYROID:					
NO. EXAMINED	5	5	5	5	5
NO. NORMAL	2	0	1	5	2
-cyst(s), NOS	3	2	4	0	3
-hypertrophy, follicular epithelium					
minimal	0	1	1	0	1
mild	0	2	1	0	1
moderate	0	2	0	0	0
Total Incidence, All Grades	0	5	2	0	2
-irregular/cystic follicles					
mild	0	1	0	0	0
moderate	0	1	0	0	0
Total Incidence, All Grades	0	2	0	0	0
-follicle(s), decreased size					
mild	0	1	0	0	2
moderate	0	2	1	0	0
Total Incidence, All Grades	0	3	1	0	2

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Table 2
Histomorphologic Observations in the Thyroid Gland

Dose Group:	1	1	1	1	1	2	2	2	2	2
Target Dosage (mg/kg/day)	0	0	0	0	0	50	50	50	50	50
Animal Number:	6726	6727	6728	6729	6730	6731	6732	6733	6734	6735
Sex:	F	F	F	F	F	F	F	F	F	F
THYROID:										
-cyst(s), NOS	P	P	-	-	P	-	-	P	P	-
-hypertrophy, follicular epithelium	-	-	-	-	-	1	2	3	2	3
-irregular/cystic follicles	-	-	-	-	-	3	2	-	-	-
-follicles, decreased size	-	-	-	-	-	-	-	3	2	3

Dose Group:	3	3	3	3	3	4	4	4	4	4
Target Dosage (mg/kg/day):	100	100	100	100	100	10	10	10	10	10
Animal Number:	6736	6737	6738	6739	6740	6741	6742	6743	6744	6745
Sex:	F	F	F	F	F	F	F	F	F	F
THYROID:										
-cyst(s), NOS	P	-	P	P	P	-	-	-	-	-
-hypertrophy, follicular epithelium	1	-	-	-	2	-	-	-	-	-
-follicles, decreased size	-	-	-	-	3	-	-	-	-	-

Dose Group:	5	5	5	5	5
Target Dosage (mg/kg/day):	20	20	20	20	20
Animal Number:	6746	6747	6748	6749	6750
Sex:	F	F	F	F	F
THYROID:					
-cyst(s), NOS	P	P	-	-	P
-hypertrophy, follicular epithelium	2	-	-	-	1
-follicles, decreased size	2	-	-	-	2

KEY:
- - = Not remarkable (within normal limits or indicated change or lesion not present)
- P = Indicated change or lesion present
- 1 = Minimal degree or amount of indicated change
- 2 = Mild degree or amount of indicated change
- 3 = Moderate degree or amount of indicated
- 4 = Marked degree or amount of indicated change

ATTACHMENT 4

QUALITY ASSURANCE UNIT PILOT REPORT STATEMENT

RESEARCH Argus LABORATORIES

Argus Research Laboratories, Inc.
905 Sheehy Drive, Building A
Horsham, Pennsylvania 19044
T: (215) 443-8710 F: (215) 443-8587

QUALITY ASSURANCE UNIT PILOT REPORT STATEMENT

Study Director: Raymond G. York, Ph.D., DABT

Executive Director of Research: Mildred S. Christian, Ph.D., ATS

Protocol 1416-002P: Oral (Drinking Water) Dosage-Range Developmental Toxicity Study of Ammonium Perchlorate in Rabbits

The draft protocol for this study was audited for adherence to U.S. Environmental Protection Agency (EPA FIFRA) Good Laboratory Practice Standards, U.S. Environmental Protection Agency (EPA TSCA) Good Laboratory Practice Standards, Organization for Economic Cooperation and Development (OECD) Good Laboratory Practice in the Testing of Chemicals and Japanese Ministry of Agriculture, Forestry and Fisheries (MAFF) Good Laboratory Practice Regulations between 03 DEC 97 and 04 DEC 97.

Critical phases of this study were inspected four times; study information and raw data were audited twice (see tables 1 and 2 for dates and phases/data).

The draft pilot report and the raw data for this study were compared and audited for accuracy, for adherence to protocol requirements, and for adherence to U.S. Environmental Protection Agency (EPA FIFRA) Good Laboratory Practice Standards, U.S. Environmental Protection Agency (EPA TSCA) Good Laboratory Practice Standards, Organization for Economic Cooperation and Development (OECD) Good Laboratory Practice in the Testing of Chemicals and Japanese Ministry of Agriculture, Forestry and Fisheries (MAFF) Good Laboratory Practice Regulations between 03 MAR 98 and 25 MAR 98, and for revisions requested by the Sponsor 08 DEC 98 and 10 DEC 98.

This study was conducted according to U.S. Environmental Protection Agency (EPA FIFRA) Good Laboratory Practice Standards, U.S. Environmental Protection Agency (EPA TSCA) Good Laboratory Practice Standards, Organization for Economic Cooperation and Development (OECD) Good Laboratory Practice in the Testing of Chemicals and Japanese Ministry of Agriculture, Forestry and Fisheries (MAFF) Good Laboratory Practice Regulations.

Barbara J. Patterson 10 Dec 98

Barbara J. Patterson, B.A. Date
Director of Operations
and Compliance

Heather L. Rabattini 10 Dec 98

for Lisa A. Zaborowski, B.S. Date
Senior Quality Assurance Associate
and Principal Auditor

TABLE 1

CRITICAL PHASES INSPECTED

Test Substance Preparation

Date of inspection: 30 DEC 97

Date results reported to the Study Director and Management: 06 JAN 98

Test Substance Administration - Drinking Water

Date of inspection: 30 DEC 97

Date results reported to the Study Director and Management: 06 JAN 98

Caesarean-Sectioning

Date of inspection: 15 JAN 98

Date results reported to the Study Director and Management: 22 JAN 98

Blood Collection

Date of inspection: 15 JAN 98

Date results reported to the Study Director and Management: 22 JAN 98

TABLE 2

RAW DATA AUDIT(S)

The following study information and raw data were audited on 31 JAN 98:

Protocol.
Protocol amendments.
List of personnel.
Animal receipt, randomization, and acclimation.
Veterinary examination.
In-life transaction record.
Feed consumption.
Water consumption.
Caesarean-sectioning.
Maternal gross observations.
Fetal gross observations.
Organ weights.
Tissue packing lists.
General comments.
Study maintenance records.
Tempscribes.
Feed and water analyses.
Edit requests.
Data review page.
Blood collection data and packing lists.
Back entry data confirmation.
Error codes and codes for critical observations.

The results of this audit were reported to the Study Director and Management on 02 FEB 98.

The following study information and raw data were audited on 08 FEB 98 and 25 FEB 98.

Test substance receipt, preparation and use.
Test substance packing lists.

The results of this audit were reported to the Study Director and Management on 26 FEB 98.